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Nature, Nurture, and Nutrition

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It was during that over-determined period of materialism, at the mid-point of the 19th century that Ludwig Feuerbach remarked: "Man is what he eats." A remark which if not altogether silly, is nearly so, for man is what he is, not because he eats what he eats, but because he is the most educable of all the creatures upon the face of the earth. It is not edibility which makes man, but educability.

Those who are concerned with human nutrition must be continuously alive to the fact that it is the human aspect of the equation rather than the nutritional which is the more important. The human aspect of the equation is the more important not simply because it is the more difficult to understand and to manage, but because it is the most significant factor in determining the nutritional behavior of human beings. As we shall see, the schemes of men go oft agley because of their failure to take the human factor full roundedly into consideration.

I have been asked, as an anthropologist, to discuss some of the cultural psychologic aspects of the problems attaching to food, with a view to bringing into high relief something of the nature of the creature with whom nutritionists have to deal, hence, the title of this paper, "Nature, Nurture, and Nutrition."

NATURE

By nature man is the most adaptively versatile of all creatures. In so far as food is concerned, the fact is that anything that is edible has constituted food at more than one period of man's history and in more than one human group. Today this is still true of the non-literate peoples who live at the subsistence level in many different parts of the world, such, for example, as the Australian aborigines, the Eskimo, the Bushmen of South Africa, the Andaman Islanders, and the tribes of Tierra del Fuego. It is not merely that these peoples eat what they *think* is edible, but that they eat everything that is in fact edible.

By nature, then, there is no food that man cannot eat, and in fact, in certain human societies, does not eat. How then does it come about that so universal an eater can become as ornery as he does about the foods he will eat and those he will not? The answer is: Nurture, or what the anthropologist calls *culture*.

NURTURE

Even among the non-literate peoples I have mentioned, ideas relating to the qualities of food and their significance for human welfare are present. Indeed, these ideas are often more complexly developed than their equivalents in more civilized societies. For example, among the Andamanese foods that are difficult and dangerous to procure, such as dugong, the *komara* fish, some snakes and the like, are considered dangerous to eat. Other foods, considered less dangerous, are nevertheless assigned a rated danger value on the food scale. Immediately after the consumption of such foods, it is the custom to decorate the body with white clay. Failure to do so, it is avowed, would lead to more or less severe illness. Since the procurement of food is the principal

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social activity of the Andamanese it is believed that the painting of the body after the consumption of the "dangerous" foods is a ritual solemnizing the recognition not only of the value of food, but of the social bonds which through food relate one to one's fellows.*

This socially binding aspect of food is encountered in all human societies. It persists even in our own atomized societies of the western world, in which the individual and the group tend to become separated from any profound understanding of the meaning of the institutions and customs which characterize the group. We still tend to recognize that a meal is a socially binding occasion, that "to break bread" with the stranger is to transform him from a stranger and possibly an enemy into a neighbor and friend. We generally like to discuss matters of moment over a meal, for men are persuasively at their best at such times. In order to prepare the members of an audience for the benevolent reception of a talk such as this, we generally provide them with relaxing liquids and quasi-stupefying foods, the one acting as a vaso-dilator resulting in a warm capillary glow, the other producing a reduction in CCC—the coefficient of critical consciousness.

But that is to put it somewhat crassly. In more human terms we recognize that a good meal is likely to bring the group more closely together, and thus more agreeably and securely achieve its purposes. In passing it may be remarked that the physiologic and psychologic bases underlying the sociality of the group meal would more than repay investigation—particularly in a society in which the institution of the family meal appears, like so much else, to be breaking down.

In all human societies ideas influence what men do about food. These ideas are usually transmitted to the individual by an already existing tradition. So that what one eats, how one eats, where and when one eats is largely culturally conditioned. Thus it is principally the habits in which he has been nurtured that determine how the individual shall behave in relation to the consumption of food, as the advertising confraternity so well understands.

It seems natural to many Americans to begin the day with a cup of coffee and a cigarette. But coffee and cigarettes are obvious examples of habits which have been learned in a particular culture, and are quite unknown in other cultures, just as coffee was unknown in Europe till the late 17th century, and cigarettes until the late 19th century. Though clearly artificial habits, and certainly not natural in any sense of the word, it is very necessary to understand that such artificial habits can become a powerful second nature, which is virtually as strong as any of the natural drives. It is the recognition of this fact that is essential if one is to understand the character of the forces with which one is dealing in the field of practical nutrition.

Just as the making of a good human being starts in the home, so does the establishment of good nutritional habits. These are not likely to be achieved in a home in which the mother, puffing on a cigarette between sips of coffee, feeds her baby from a bottle. The only advantage accruing to anyone in such a relationship is that the bottle-fed baby doesn't get as much cigarette ash in his eyes as the breast fed baby. Indeed, perhaps no more cogent illustration could be found of the profound desensitization to human need into which our society has fallen than our attitudes toward breastfeeding. We have lived to hear so-called experts tell us that no woman, who doesn't want to, need feed her baby, and that any good doctor can prepare a formula that is as good as mother's milk. I have heard experts say, and the general run of physicians echo their statement, that colostrum is a useless liquid, hence there is no reason for putting the baby to suck at its mother's breast until the transitional milk begins to come in.

Such statements and the beliefs to which they give rise exhibit not only a shocking ignorance of the clinical comparative biochemistry and immunology of colostrum and mother's milk, but what is equally destructive, they exhibit a failure to recognize the important biosocial and psychobiologic factors and relationships

* See A. R. Radcliffe-Brown, *The Andaman Islanders*, New York, Cambridge University Press, 1922, p. 267 et seq.

which obtain in the undisturbed maternal-infant nutritional situation.

I dwell on our contemporary handling of the maternal-infant situation because it so strikingly demonstrates the nature of our failure—namely, the *understanding of the situation as a whole*, the understanding of the fact that there is no substitute for the "milk of human kindness," that the best of bottle formulae, cannot make up for the substantive psychologic and biologic losses suffered by both the artificially fed infant and its mother.

It is beyond all other things necessary to realize that the problem of nutrition is fundamentally a cultural problem. By culture the anthropologist understands the man-made part of the environment, whatever is invented, transmitted, and perpetuated—in other words, the socially acquired habits of man. Man's past working together with the present to mould man's future!

Because the problem of nutrition is largely a cultural one, the approach to its solution must be principally through cultural means. But what is the problem of nutrition which we are concerned to solve? It is, surely, how one can get human beings to eat foods which at every stage of their growth and development are those most likely to contribute to their optimum health. The achievement of this is, surely, the goal to which all the activities of nutritionists are directed.

Toward the attainment of this goal I think it would be wise were nutritionists to acquire unto themselves an anthropological dimension. I can best illustrate the necessity for this by citing some actual examples.

No matter how complete our knowledge of the biochemistry, the physiology, and the nutritional value of food may be, unless we attend to the sociopsychologic or cultural factors first we are not likely to succeed in our endeavors. This is what the following experiences in the field illustrate.

In the first place I should like to refer to Goldberger's famous discovery of the cause of pellagra. Pellagra, as you know, is a severe nutritional disorder due to a deficient intake of nicotinamide. In 1914 when Goldberger was sent South by the U. S. Public Health Service to investigate the disease somewhere in the vicinity of 200,000 persons in the southern states were suffering from pellagra. Pellagra was soon shown to be a disease of the "Three m's": maize, meal, molasses, and meat (salt pork), a diet associated with poverty and an insufficiency of the anti-pellagra vitamin. In 1955 less than 500 cases of pellagra were reported for the whole of the United States, most of these cases still being reported from the southern states.

The important point to note here is that pellagra is a disease of poverty, and that with improvement in standards of living, pellagra becomes a vanished disease. Pellagra is not so much a vitamin deficiency disease as it is a socio-economic deficiency disease. The vitamin deficiency follows upon the socio-economic deficiency, rather than the socio-economic deficiency following upon the pellagra, although that happens as a tertiary result, too. The principal condition is the socio-economic deficiency, the poverty which leads to an inadequate diet, which leads to the deficiency, which leads to the disease.

To make pellagra an unknown disease, all that one has to do is to raise the socio-economic standard of living in the areas in which it is endemic—nothing more, nothing less.

If we would improve upon the nutrition of the socio-economically depressed segments of the population, we can best do so by providing them with better opportunities to elevate their socio-economic status. Pellagra, in the United States, has in part been reduced by this means and also in part by the making freely available of the information and the reasons for adhering to a well-balanced diet.

But reason sometimes does not appear to be enough. Upon analysis, however, it is usually found that it was not a case of reason not being enough, but of reason not having been carried far enough, as the following case report may serve to illustrate.

In 1946, after what appeared at the time to have been a thorough survey of the situation, a county extension agent of the United States Department of Agriculture succeeded in interesting the Spanish American farmers in the Rio Grande Valley of New Mexico in the

substitution of hybrid corn for their own poor Indian variety.

The native corn is of poor quality and poor yield, while the hybrid corn is of excellent quality and yields about three times as large a crop as the native variety. Forty of the 84 growers in the village planted hybrid corn the first year and doubled the production per acre of the preceding year. The following year 60 growers planted hybrid corn, but in 1948, although the high yield had continued, only 30 farmers planted hybrid corn. The other thirty returned to the traditional variety. In 1949, there were only three farmers planting hybrid corn. All the rest were planting the old variety of corn.

The county agent was on good terms with the farmers, spoke their language, and was interested in their welfare. He had carefully studied their problems, discussed them with the leaders, and then presented his plan at a special meeting. He showed movies and cartoons illustrating the advantages of the hybrid corn. There was a free discussion and everyone had agreed upon the advantages of the new corn. A demonstration plot was set up showing the threefold yield of the new corn as compared with the old. The new seed was made available in exchange for the old.

The yield, quality, and appearance of the hybrid corn planted by the farmers fulfilled all the promised expectations. Why then did they cease to plant it? The answer is very simple: Never underestimate the power of a woman. Their wives didn't like it. "My wife doesn't like that hybrid, that's all." That was the answer.

The corn had not been popular from the first harvest. All the wives had complained. Its texture was wrong; it didn't hang well together for tortillas; the tortillas came out the wrong color. Few had cared for the flavor. But though it made abundant food for the animals, and there was even a hope that one might get used to the taste, the flavor and texture, and the revolt of the wives constituted a combination of conditions which could not be resisted. So the farmers, after having tried their best, returned to the Indian corn. Domestic harmony was restored, tortillas looked and tasted as they should, and once again custom declared itself king.

The story is a common one. But let us examine this particular nutritional tragi-comedy and attempt to discover what went wrong, and how a happier denouement might have been brought about.

The county agent had made a study of the physical conditions, the economic conditions, the environment, and the farming practices. He had concluded that increased farm production could greatly benefit the community. He had obtained the agreement of the farmers to this conclusion. All seemed to be well.

Now let us see what he failed to do.

He failed to inquire into the food habits of the people.

He failed to inquire into the uses to which the corn was habitually put.

He failed to recognize that there might be a problem of taste.

He failed to recognize that the customary courtesy of the people prevented them from expressing themselves freely in the presence of an expert, and thus failed to learn what some of the problems might be which could have been forestalled.

He failed to reckon with the preparers of food, the women, and thus paid the penalty of those who ignore the fact that women constitute at least one-half of the human race.

In the light of this *post mortem* it has been suggested that a possibly successful procedure would have included the following steps:

(1) Trial of several varieties of hybrid corn in full recognition on the part of everyone that this was experimental, in order to discover which corn the people liked best. (2) Testing to see how the corn selected really fitted into the culture patterns. (3) Continued working together with the farmers in order to see that they fully convinced themselves of the advantages of the new corn. (4) Continued contact to obviate all difficulties and to make any necessary modifications. By such means the taste problem might have been forestalled and met, and the society as a whole benefited.

This case report presents a good illustration of what I mean by the approach to the nutritional situation as a whole, and particularly

from the cultural point of view. But what cases such as this should teach us* is not that it is difficult to modify food habits, but rather that with the proper approach, it is probably possible to modify any habit, whether of food or otherwise. The whole of human history, and especially recent history, stands as a testament to that fact. Perhaps no better illustration can be given of the modifiability of human food habits than that which is afforded by the history of the potato.

Brought back from Peru by Spanish explorers in the 16th Century, it was at first rejected by Europeans. The rumor was soon spread that it poisoned the ground and caused diarrhea. That the potato first took root in Ireland was due entirely to the condition of virtually continuous famine to which the populace had been reduced by the English. Introduced into Ireland by Sir Walter Raleigh, potatoes were being widely cultivated and eaten by the middle of the first half of the 17th Century. As is well-known, the potato became the staple food of the Irish, and it was to the tragic failure of the potato crops in the middle of the 19th Century that Boston owes so great a part of its population. The Irish undoubtedly took to the potato not because they originally liked it, but because they were reduced to it. It took the English another half century before they accepted the humble tuber, and the rest of Europe took even longer before it succumbed. *The History and Social Influence of the Potato* (New York, Cambridge University Press, 1949) has been ably written by Dr. Redcliffe N. Salaman, its vicissitudes and eventual conquest being fully set out in the book of that title. The ruses by which people were persuaded to overcome their prejudices and eat the potatoes they had cultivated forms an entertaining chapter in the history of nutrition.

As late as 1771 the potato was held so much under suspicion, that the French government appealed to the Medical Faculty of Paris for its considered judgment. The Faculty returned a report to the effect that the potato was a good and healthy food, in no way injurious to health, and of great utility.

In Prussia it was the general belief that the potato gave rise to scrofula, rickets, and consumption, among other evils. It required all the influence that Frederick the Great could bring to dissolve this prejudice. When Frederick sent a wagon-load of potatoes to Kolberg in 1774, after the famine, in the hope that the people would grow potatoes themselves, the answer he received was: "The things have neither smell nor taste, not even the dogs will eat them, so what use are they to us?" The opposition was overcome by sending a uniformed Swabian gendarme who, by persuasion and example, taught the people how to cultivate and grow the tubers.*

Benjamin Thompson, Count Rumford (1753–1814) who, as a Royalist had to leave his native Massachusetts in 1776, in later years as head of the army and ordinance of the Elector of Bavaria, ingeniously introduced the cultivation of the potato into that country by ordering every soldier to plant and cultivate a patch of potatoes, and also to cook and eat them. The length of military service gave the soldier more than enough time for raising tubers and developing a taste for them. When the men returned to their farms and villages potatoes came at last into their own.

The opposition to the potato and to other new kinds of foods raises an interesting question: "What is the mechanism behind such opposition?" In the case of the potato Salaman suggests that the fear of disease was simply a rationalization of unconscious fears, the fear of breaking with a bible-permeated common tradition, and of the eating of a new food that was akin to eating the forbidden fruit of the Garden of Eden, "a sinful act which, even if its effects were physically harmless, was bound to create a feeling of personal guilt, which demanded some kind of expiation lest the individual be smitten with some dreaded disease." (Salaman, pp. 115–116).

* For this and other such cases see Edward H. Spicer, editor, *Human Problems in Technological Change*, "Introduction of Hybrid Corn to Spanish American Farmers in New Mexico," by Anacleto Apodaca, Russell Sage Foundation, New York, 1952, pp. 35–39.

* Bruford W. H., *Germany in the Eighteenth Century*, Cambridge University Press, New York, 1935, pp. 115–116.

That such unconscious motivations are often involved in the individual's response to certain foods has now a well-authenticated body of case histories and knowledge to support it. Such knowledge has led, for example, to a revolution in the way meat is packaged and displayed in our food markets, owing to our better understanding of the unconscious avoidance reactions of young housewives when meat is dealt with in the old manner.

The resistance to this day in Europe to Indian corn as a food for human beings is based largely on the fact that it is believed to be a food fit only for hogs and cattle to eat. Since I myself believed this for the first 21 years of my life, and am now a perfervid corn eater, I stand before you as a living example of a regression either to the barnyard or of progression in the art of eating without a knife and fork.

Man by virtue of his great plasticity or what I have earlier called educability, is able to learn new habits and unlearn old ones.

It is well known, and has been repeatedly demonstrated by test, that the unlearning of habits becomes more difficult with age, particularly when the habits are enjoyable ones. Furthermore, we know that it is well nigh impossible to unlearn a habit one enjoys in the absence of a sufficiently compelling motivation. For example, the knowledge that they may develop cancer of the lung does not constitute a sufficiently compelling reason to cause millions of smokers to relinquish the habit. On the other hand, some thousands of smokers have abandoned the habit; but here we cannot be certain that the compelling reason was the knowledge that they might develop lung cancer. That piece of knowledge may merely have been, so to speak, the lucky strike that broke the camel's back. Virtue may be its own reward, but the new non-smoker often finds that in escaping from the threat of cancer he has become a victim of the menace of corpulence. No wonder so many erstwhile smokers prefer to resume their chances on the roundabouts with the possibility of cancer than to continue on the swings with the certainty of corpulence.

May it not be that the great increase in smoking in this century is related to, among other things, the great reduction in breast feeding and the inadequate satisfaction of bottle-feeding?

These remarks, made in passing, are not unrelated to the work of the practical nutritionist. But we cannot stop to develop them here. What I was getting round to when I began the discussion of habits was that in view of the difficulty of unlearning early habits, it were surely the course of wisdom to create good habits in the early years of the child's development. Taking the world as we find it, and speaking for our culture alone, it seems to me that it is through education that our people can best be taught how to eat as they should.

We have succeeded in teaching pregnant mothers that the most important part of their regimen, during the $265\frac{1}{2}$ days of pregnancy, for the health of the child, is a good well-balanced diet. We have also succeeded in getting across to that half of the human race that is sufficiently motivated, namely women, that there are such things as calculable calories and measurable vitamins, and that they affect not only the shape of things to come but also their desirability as well as durability. It has long been known that women are much more careful of the foods they eat than men. And since women are the mothers of mankind and the purchasers and preparers of food in our culture, it is principally through them that we are most likely to succeed in influencing the nutrition of the people. Hence, while by no means neglecting the male, it would seem that the most effective approach to his stomach would be *via* his mother during childhood and through his wife during technical adulthood.

Since mothers are the persons in our society who are pivotally involved in the nutrition of the family, it is through them that the teaching of good nutritional habits is most likely to succeed. And this for several reasons which are almost too obvious to discuss. But discussed they must be. Firstly, mothers are most desirous of doing their best by their children. If they are told by the experts of one period that spinach is the thing, spinach will be the thing. If they are informed by the experts somewhat later that spinach is not the thing, spinach will cease to be the thing. If candy is shown to be

bad for the teeth, they will do what they can to regulate the consumption of candy and purchase anti-caries candy. If meals should be served, representing on the plate a good proportion of the colors of the spectrum, they will see to it that this is done. It is really quite true that since he could not be everywhere, God created mothers. Thus, the first point to recognize is that in so far as nutrition is concerned mothers are probably the most educable members of the population.

Secondly, being the most educable members of the population, and being the principal feeders of the young, mothers are most likely to be the ones to modify and change food habits in the desired direction.

Thirdly, not only is the nutrition of the child largely determined by the mother, but good food habits are placed on a firm foundation throughout childhood and adolescence by the mother's conduct not only in feeding her children but in feeding herself and her husband. The dietary example set by the parents plays an important role in influencing the dietary habits of the child. Hence the training of prospective parents in this regimen is extremely important.

One of the greatest obstacles to the achievement of an optimum nutrition for every individual in our culture is the fragmentation of social relationships which is steadily occurring within the family itself. All but the mother's activities tend to be directed away from, rather than toward the family. Instead of being family-centered, the activities of the non-material members of the family are directed toward work, interests, and play outside the home. Children are sent off to school with their peanut sandwiches and apples; the husband, in millions of cases, takes his own variety of sandwiches and flask of hot coffee to work with him, and even the mother herself, left alone as she is during the greater part of the day when her children are of school age, munches on snacks rather than prepare an adequate meal for herself. When the children return from school they are ready not for a meal but for some snacks and candy. In the majority of cases they will eat their dinner before father returns from work And when they are adolescent they will have too many outside interests to be able to adjust their mealtimes to those of their parents. Their diets are likely to consist largely of soft drinks, hamburgers, ice-cream, coffee, and cigarettes. Is it any wonder that we are not a particularly healthy nation?

A recent survey, conducted by the Youth Research Institute, found that only 29 per cent of 4,310 teen-agers dined regularly with their parents, "regularly" meaning more than three times a week. Another survey of 3,517 children from 5 to 12 years of age revealed pretty much the same facts.

I would suggest that the means of re-establishing the family meal might well be worth looking into, not merely as a contribution to better nutrition, but to better family and social relationships.

Into the psychologic significances of overeating I cannot enter here. Mostly the phenomenon is due to disturbed social relationships, and these must be corrected before anything of enduring value can be done for such cases. There is, however, a form of overeating to which I would briefly like to refer. This is the overeating of the average adult.

Most of us overeat. The quantities of food we consumed during the first 25 years of our lives were perhaps necessary for an actively growing organism. But as we grow older we require less food to maintain ourselves in optimum health. Nevertheless, most of us persist in consuming the same or even greater quantities of food than we did in our earlier years. Here again is a fertile field for research. How can we deal with adult habits of eating? It is a problem the approach to which I must leave to you.

It was Socrates who said: "Bad men live that they may eat and drink, whereas good men eat and drink that they may live." Perhaps he had something there, for if we substitute for "bad," "feverishly driven," we may know where to seek for the answer to this problem.

Humanity asks the question: "Canst thou minister to a hungry soul?" And adds, "Ah, if to eat were as easy as to know what t'were

good to eat, peanuts had been porridge, and lobster mayonnaise the humble kipper."

I think, ladies and gentlemen, that if we set about it soundly, we can show humanity that to know what t'were good to eat, is as easy as eating itself.

Pommes Naphthalenes

"According to Dr. Wynne Roberts, the Medical Officer of Health of Flintshire (as quoted in the *Medical Officer*), potatoes with a moth-ball flavour when cooked were submitted to the public analyst, who found them to be 'wholesome.' It appears that potatoes grown in fields that have been subjected to treatment by certain insecticides will sometimes give a moth-ball flavour of naphthalene on being cooked. Since the fundamental property that gives the potato its value is that it is palatable and therefore edible, and since *pommes naphthalènes* must be nauseating, it seems a little irrelevant to worry about whether it is wholesome or not."
—*Med. Press* 234: 487, 1955.

Serum Cholesterol in Japanese Coal Miners

A DIETARY EXPERIMENT

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IN CONNECTION with a study of the relationship between the mode of life and the concentrations of cholesterol and lipoproteins in the blood serum in Japan, it was important to decide whether the low serum cholesterol found to be characteristic of the Japanese men could be ascribed to the diet. An independent dietary survey at Shime (near Fukuoka, Kyushu, Japan) confirmed the very low-fat content of the average diet as reported from Japanese national surveys.[1] Only 10.3 per cent of the total calories of the miners were provided by fats in the diet. The sources of the fats are summarized in Table I.

While the diet would seem to be an adequate explanation for the serum cholesterol values, it was decided to see whether the addition of a moderate amount of fat to the diet would, in fact, raise the serum cholesterol level. The results of a brief experiment on a group of these miners are summarized below.

SUBJECTS AND PROCEDURE

Twenty-one apparently healthy Japanese coal miners 22 to 54 years of age were recruited in the small mining town of Shime. All were engaged in their usual hard work underground at the coal face. It was arranged that their customary mode of life would be maintained without change except that for 11 days they would modify their diet to replace about 700 cal of their daily rice with 50 g of butter or margarine, two slices of bread and a serving of water ice (sherbet) all adding up to the calorie equivalent of the displaced rice. They insisted on the bread to help them eat the fat, which they generally dislike, and the water ice (sherbet) was our answer to their request for a sweet (dessert) to offset the taste of the fat.

TABLE I

Fats in the Average Coal Miner's Diet at Shime, Japan, in April 1956. The Table Gives the Percentages of the Total Fat Calories From the Various Food Sources

Rice	17.0%	Fish	32.5%
Soy bean	11.3	Eggs	15.2
Sesame, rape seed	4.9	Marine invertebrates	4.3
Misc. vegetables	4.0	Butter	3.9
Wheat	2.7	Beef	3.0
		Whale oil	1.2
All veg. sources	39.9%	All animal sources	60.1%

Blood samples were taken from arm veins twice, two days apart, just before the diet change, after four and eleven days on the diet and again two weeks after resuming their usual diet.

After the bloods had clotted, the serum was pipetted off and two or more 0.1 ml portions of each sample were measured out on Whatman's No. 1 filter paper and dried by hanging

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up the papers in the air at room temperature (14° to 20° C). Additional 0.1-ml portions were measured out for paper electrophoresis for 15 hr at 185 volts by the method of Anderson and Keys.[2] After the electrophoresis was completed the paper strips were air dried in the same manner as the whole serum samples. The dry paper strips and serum samples were all sent by air mail to the Laboratory of Physiological Hygiene in Minneapolis where they were analyzed for total cholesterol and for cholesterol in the alpha and beta lipoprotein fractions as separated by paper electrophoresis, using the methods of Anderson and Keys.[2]

A detailed study of the ordinary diet of the miners at Shime was carried out by making household inventories and recording food purchases for a week. The diets of different families conformed to a very constant pattern in which proteins provided an average of about 13 per cent and fats about 10 to 12 per cent of the total calories. The extra fat eaten during the experiment raised the average fat intake from 10.3 to 24.9 per cent of the total calories.

The 21 men were divided into three groups of seven men each matched in regard to age, relative body weight, and fatness (judged from the thickness of the subcutaneous fat over the triceps muscle and over the tip of the scapula). In each group there were two men in the twenties and five men in the forties and early fifties. Group B received fresh butter as the added fat. Group AM received margarine made largely or wholly from animal fats, while Group VM received a margarine made exclusively from vegetable oils.

In Japan, as elsewhere, manufacturers are reluctant to disclose the exact composition and details of ingredients in their margarines. We were assured, however, that the hydrogenation and other procedures are exactly the same as used in the United States and in Europe and, indeed, the appearance, texture and taste of both margarines was comparable to the common colored margarines of the United States. The animal fat margarine (Snow Brand) was stated to be made largely from whale oil together with beef and pork fat and some vegetable oils. The vegetable margarine (made by the same manufacturer in Hokaido) was emphatically stated to be made exclusively with vegetable oils; this is an important consideration for some religious groups in Japan.

Samples of these margarines were sent by air mail to Minnesota and there stored in the cold until they were sent to the Research Division of the Procter and Gamble Co., in Cincinnati, Ohio, where detailed analyses were made. The essential data, together with average data for butterfat and for a U. S. all-vegetable-oil margarine for comparison, are summarized in Table II. These materials were analyzed "blind" by the Procter and Gamble Research Division by the methods given in the Official Methods of the American Oil Chemists Society. The following comments are appropriate:

TABLE II

Composition of Japanese Margarines A and B, Used in the Present Experiment, and of a Typical U. S. Margarine as Analyzed by the Research Division of Procter and Gamble Co. Typical Values for Butterfat Are Also Listed

	A (Whale)	B (All veg.)	C (U. S. veg.)	Butter fat
	Fat Component			
Iodine Value	39.2	36.6	78.6	35
Saponification Value	226.0	227.7	194.2	245
Free fatty acids, %	0.1	0.6	0.1	?
Unsaponifiable, %	0.4	0.3	0.6	?
Fatty Acid Composition, %				
Saturated	65.0	63.8	21.7	65
Oleic	24.9	30.0	66.0	25
Linoleic	9.9	6.0	11.9	3
Linolenic	0.2	0.2	0.4	1
Arachidonic	0	0	0	1
Conjugated Diene	0.3	0.2	1.2	?
Trans acids, %	17.3	18.1	41.5	0
	Proximate Composition			
Water, %	16.5	14.4	14.4	15.5
Fat, %	79.9	81.2	80.3	81.0
Solids not fat, %	4.5	4.1	4.3	3.5

Margarine A: The proximate composition of Margarine A is typical of that which is seen here in the United States, except that the fat content is a little low. On the other hand, the fat used in the preparation of this Margarine is considerably different from that used in the

United States . . . It appears to have been prepared from coconut oil and some other fat. It would appear to contain from 40 to 50 per cent coconut oil.

Margarine B: Margarine B is uuite similar in composition to Margarine A and all the remarks about Margarine A can be repeated here as far as Margarine B is concerned. The only difference between the two is that Margarine B is a somewhat firmer product as indicated by the iodine value and the trans-fatty acid content.

Margarine C: The proximate composition is typical of that of a margarine seen in the United States. The analytic values, too, are typical of an American margarine. On the basis of the analytic values obtained on the fat portion, it would appear that this margarine was made from soybean oil, cottonseed oil, or a similar type of domestic oil that has been hydrogenated. The somewhat higher conjugated level in this fat indicates that it undoubtedly received some mistreatment during its processing.

RESULTS

The belief is widespread in Japan that eating fats will cause diarrhea. The subjects were therefore agreeably surprised to find they were not incapacitated from diarrhea as they had feared. However, one man did develop persistent diarrhea and the diet was discontinued on that account. Another man developed an upper respiratory infection and was also discarded as a subject. Finally, one subject withdrew, leaving 18 men for the study. Some of their control characteristics are summarized in Table III.

TABLE III

Control Means (±S.E.) for the Men in the Diet Groups. "Rel. Wt." = Body Weight as % of Average for Same Age and Height in U. S. Medico-Actuarial Table. "Skinfold" = Sum of Arm and Sub-Scapular Values. "% beta" = % of Total Serum Cholesterol in the beta Lipoprotein Fraction

Group	N	Age	Rel. wt. %	Skinfold *mm*	B.P. *mm* Hg	Serum Cholesterol	
						Total *mg*/100 *ml*	% in beta
B	7	39.1	90.0	14.8	137/86	145.4 ± 14.4	69.3 ± 3.4
AM	6	37.8	84.8	12.2	138/83	135.7 ± 11.0	67.8 ± 4.1
VM	5	43.1	84.3	13.5	134/83	163.2 ± 16.6	73.8 ± 2.6
AM + VM	11	40.2	84.6	12.8	136/83	148.2 ± 7.9	70.5 ± 2.2
All	18	39.8	86.5	13.6	136/84	147.1 ± 7.2	70.1 ± 2.0

TABLE IV

Mean (±S.E.) Serum Cholesterol Change after 4 and 11 Days on Diet with 450 cal of Rice Being Replaced with 50 g of Fat: "B" = Butter; "AM" = Animal Fat (Mostly Whale Oil) Margarine; "VM" = All-Vegetable-Oil Margarine

Group	N	Δ Total cholesterol *mg*/100 *ml*		Δ beta%
		4 Days	11 Days	11 Days
B	7	+0.43 ± 6.58	+17.57 ± 5.23	−2.6 ± 1.8
AM	6	+2.17 ± 3.65	+19.00 ± 7.98	−0.3 ± 2.1
VM	5	+8.80 ± 5.09	+14.20 ± 6.92	+1.2 ± 3.6
AM + VM	11	+5.18 ± 3.62	+16.82 ± 4.82	+0.5 ± 1.8
All	18	+3.30 ± 3.11	+17.11 ± 3.66	−0.7 ± 1.4

Since the mean difference between the pre- and post-diet control values for total cholesterol was only 2.6 mg per 100 ml with a standard error of ±2.7, the pre- and post-diet values for each man were averaged and these figures are given in Table I and were used as the control values in subsequent computations.

The principal findings in regard to serum cholesterol are summarized in Table IV. All of the groups tended to show a slight rise in total serum cholesterol after four days on the

diet but this change is not statistically significant for any of the groups or for all groups combined. After 11 days, however, the total serum cholesterol concentration had risen in all groups to about the same extent, the grand average being 17.11 ± 3.66 mg per 100 ml which is statistically highly significant (t = 4.68, for N = 18, t = 4.5 for p = 0.0003). There was no significant difference between the responses of any of the groups nor did the butter group (B) differ from the combined margarine groups (AM + VM).

The observed rise in total serum cholesterol represents a grand average increase of 11.6 per cent above the control values, ranging from 8.7 per cent for the VM group to 15.2 per cent for the AM group. This suggests a greater relative effect in the AM than in the VM group but the difference of 6.5 per cent is not statistically significant, the standard error of the difference being ±7.0 per cent.

Most of the rise in the total serum cholesterol on the increased dietary fat is obviously accounted for by the cholesterol in the beta lipoprotein fraction but the data do not allow a secure conclusion as to whether the mean alpha lipoprotein cholesterol also was actually increased. The mean rise in this fraction was + 3.00 ± 2.07 mg per 100 ml. As Table IV shows, there was no significant change in the percentage of the total cholesterol represented by that in the beta lipoprotein.

DISCUSSION

The experiment clearly shows that it is reasonable to attribute the low cholesterol values in these Japanese to their diet and it is unnecessary to invoke theories about race or physical labor as conceivable prime factors. The outstanding peculiarity of the diet, is the fact that total fats provide only about one-fourth the proportion of calories from fats currently used in the average U. S. diet (10.3 vs. 40 + per cent of calories from fats). The total calories in the diet of these miners seem to be adequate. The average intake of 3,297 cal daily is a good deal for these small men (average height 160.5 cm or only 5 feet 3 inches) even though they are doing hard work. There were no complaints of insufficient food and the men showed no signs of underfeeding. Their average relative body weight is low by United States standards but this value has little significance in these men with very small bones and whose body form is so different from that of the American. The skinfold measurements showed that these men are not fat but the values are not indicative of real undernutrition. Moreover, inspection of these men in the nude showed smooth contours and no prominent rib cages, deep supra-sternal notches or winged scapulae. Finally, the observed serum cholesterol changes occurred without changing the dietary calories and no significant weight changes were observed. Such small individual weight changes as were recorded (extremes of + 4 lb and −2.5 lb) were not correlated with the changes in the serum cholesterol.

We have observed similarly low cholesterol values in population samples elsewhere who subsist on relatively low-fat diets. Thirty-five Neapolitan steel workers aged 40 to 49 (average 4.36 years of age), with about 20 per cent of their calories from fats, averaged 158.8 mg of total cholesterol per 100 ml of serum.[3] Forty-six Sardinian coal miners 40 to 49 years of age (average 43.2 years) with an average of 24 per cent of fat in the diet, averaged 173.2 mg/100 ml.[4] Bantu workmen in Cape Province, South Africa, whose diet provides about 17 per cent of calories from fats, averaged 166.3 ± 41 mg/100 ml at average age 46.[5] These values may be compared with the average of 249.8 mg of total cholesterol per 100 ml for 103 members of the Minneapolis Fire Department aged 40 to 49 (average 43.6 years of age).[6] Their diets are estimated to provide more than 40 per cent of the calories from fats, mostly from butter fat and meats. The basic diets of these populations are, of course, very different. The Neapolitans and the Sardinians get most of their total calories from wheat, the Bantu from corn and the Japanese from rice.

It would be interesting, of course, to compare the serum cholesterol response in these men to that produced by a similar dietary change in other groups of men differing in race and occupation. There are no strictly com-

parable data at hand for this purpose but it does appear that the response to diet fat of these Japanese miners is at least roughly similar to our findings in dietary experiments in Minnesota.

Twelve physically healthy men with schizophrenia at the Hastings State Hospital in Minnesota, averaging 41 years of age, were maintained in calorie balance for four weeks on a diet in which 11 per cent of the total calories were provided by fats and on another occasion they were similarly maintained on a diet with 17 per cent fat calories, the difference in the amount of fat in the several diets being made up almost entirely of butterfat and beef fat. Before and for several months in between the experiments they subsisted on a standardized diet with 37 per cent fat calories. Their average intake on the hospital diet was 3.065 cal including 49 g. of butterfat, 70 g of meat fat and lard, and 16 g of vegetable fat (mainly cottonseed oil). On this hospital diet the grand average total cholesterol concentration in the serum prior to the start of the lower fat diets was 220.2 ± 9.4 mg per 100 ml in the fourth week. On the 17 per cent fat diets the mean change of the individuals from their preceding hospital diet values was a fall of 16.3 ± 5.5 mg per 100 ml and on the 11 per cent fat diet the corresponding value was a decline of 24.4 ± 6.9 mg per 100 ml from the previous house diet control. These values indicate a direct relationship between these diet fats and serium cholesterol which responds similarly in both the Minnesotans and in the Japanese coal miners. The picture is summarized in Figure 1.

These are short-time responses, of course, and it is hazardous to insist that the long-time effects would necessarily be identical. It seems reasonable to suggest, however, that some progression of the diet effect over time would explain the differences observed when populations on their habitual diets are compared. The experimental results at Shime and at the Hastings State Hospital indicate a difference of about 25 mg of cholesterol per 100 ml of serum associated with the dietary difference between 11 and 37 per cent fat cal maintained for only a couple of weeks. But comparing the Shime coal miners on their habitual diet of 11 per cent fat cal with the Hastings patients on their hospital diet of 37 per cent fat cal, the average difference is around 70 mg per 100 ml, i.e., almost three times as great. This might indicate the cumulative effect of long-time persistence on the two types of diets.

There is, of course, a major difference between the 11 per cent fat calories diet used by the Japanese and that used in the Hastings experiment. The fatty acids in the Hastings low-fat diet were something like 50 per cent saturated and less than 10 per cent represented linoleic and polyethenoid acids while the corresponding figures for the Japanese diet are less than 20 per cent saturated and perhaps 40 per cent polyethenoid acids. These differences may make an important contribution to the picture in the overall comparison of the populations on their native diets. But it should be observed that both at Hastings and at Shime the cholesterol differences were experimentally produced by changing the amounts of the more saturated fats (butterfat and beef fat) in the diet. Hence the comparison in Figure 1 has validity in demonstrating that the miners and the patients respond similarly to changes in the amounts of the same types of fats in the diet.

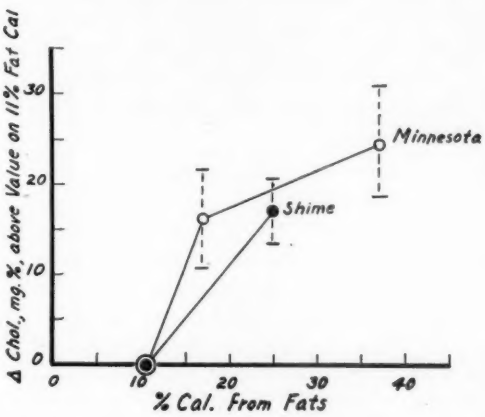

Fig. 1. Serum total cholesterol concentration at different levels of fat in the diet, expressed as the mean difference (and standard error) for the same individuals, from their values on a diet providing 11 per cent of the total calories from fats.

SUMMARY

Eighteen Japanese coal miners at Shime, Japan, were studied before, during and after a dietary experiment in which, for 11 days, their habitual diet was altered by the isocaloric substitution of 50 g of butter or margarine for a part of their customary rice. Seven of the men received butter, six of them had a margarine made from animal fats (mainly whale oil) and five received an all-vegetable margarine. The iodine values of these added fats were: butter 35, margarine A 39, vegetable margarine 37 and the corresponding contents of linoleic acid glyceride were 3, 10 and 7 per cent. The extra fat raised the average intake of these miners from 10.3 to 24.9 per cent fat cal. Their work and other living habits were unchanged.

The dietary change produced an average rise of 17.1 ± 6.6 mg of total cholesterol per 100 ml of blood serum and there were no significant differences between the effects of the several fats. The control cholesterol average was 147.1 ± 7.2 mg. per 100 ml so the rise was 11.6 per cent in 11 days. Separate analysis of the cholesterol in the alpha and beta liporotein fractions showed no significant change in the distribution resulting from the dietary change.

Comparison with dietary experiments in Minnesota indicated that the response seen in these Japanese men was comparable to that observed in Minnesota men.

ACKNOWLEDGMENTS

We are grateful to the management of the coal mine and especially to the miners at Shime whose fine cooperation was essential to the success of this work. Drs. Lloyd W. Beck and F. H. Mattson of the Research Division of Procter and Gamble Co., Cincinnati, Ohio, made the analyses of the margarines. Mrs. Margaret Haney Keys, Dr. Nobuki Endo, Dr. J. T. Anderson and Mrs. Nedra Foster were responsible for the cholesterol analyses.

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The Metabolic Availability of Glucose Monoaleuritate*

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THERE is a definite need for an infusion substance of high caloric value which will be completely non-toxic. In the past, several avenues of approach have been utilized to supply calories to patients who are unable to take food by mouth. These were infusions of sugars in high concentrations, alcohol, and emulsified fats.

Fat emulsions have been prepared from various natural fats and oils. Because of the high interfacial tension between oil and water, some surface-active agent must be added so that stable emulsions of sufficiently small particle size can be achieved. In general, these emulsifying agents are toxic in direct proportion to their surface active properties. One of the emulsifying agents, soy bean phosphatide, is precipitated by gamma globulins and incites granuloma formation when injected without fat.[1,2] It is difficult to understand why a precipitable stabilizing agent should act as a satisfactory emulsion stabilizer. Even if *in vitro* emulsion stability can be achieved, the incidence of toxic reactions in clinical tests is so high that this factor seems to preclude the possibility that emulsions will ever be safe enough for clinical use. The intravenous fat emulsions are pyrogenic[3–5] and mildly hemolytic.[5,6] The thermogenic response after infusions of emulsions occurs in such a high percentage of patients (over 15 per cent) that some authors believe all calorogenic benefits are lost if a febrile episode ensues.[7] This is comprehensible since the basal metabolic rate increases about 13 per cent for every degree centigrade rise in the body temperature.

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In addition to these major disadvantages, there are a host of minor and infrequent major toxic reactions including the occurrence of thrombocytopenia of a serious degree. The reader is referred to an excellent review by Freeman.[8] Because no clinically satisfactory intravenous-fat emulsions have been forthcoming after ten years of extensive research and clinical trials, it seems doubtful whether this approach will ever be productive of an infusion substance satisfactory for routine clinical use.

SURFACE-ACTIVE SUBSTANCES

Several water-soluble fatty acid derivatives were investigated with the view of circumventing the difficulties inherent in fat emulsions. The present investigation was begun with a study of the readily available "spans" and "tweens." These substances are polyalcohol esters of fatty acids and some of them are water-soluble. They are used commercially as non-ionic detergents, and emulsifying agents. When these substances are administered parenterally, they are highly toxic and hemolytic. It is interesting that the body can handle the fatty acid alone, or the polyalcohol moiety, yet the combination proves highly toxic. In 1912, Bloor[9] prepared several polyalcohol esters of fatty acids including glucose monoaleuritate. These substances turned out to be toxic on intravenous injection. Polyalcohol esters of fatty acids are toxic because of their surface activity or detergency. Surface-active molecules have a tendency to lower the interfacial tension between water and lipids. In other words, they tend to disperse the lipids into the surrounding aqueous medium. It happens that lipid is an essential part of cell membranes. For example, the cell membrane of the erythrocyte is composed of an outer

and inner layer of protein which is absorbed onto a bimolecular layer of lipid. The lipid is so oriented that the fat-soluble portions of the lipid molecules engage one another, and the water-soluble portions of the molecule engage the protein on the inside and outside of the cell membrane. Detergents disperse or pull the lipid portion of the cell membrane into the surrounding aqueous medium and literally disrupt the cell, causing cytolysis. In lesser concentrations, the surface-active agents may so alter the membrane permeability of the cell as to cause secondary hemolysis in the case of erythrocytes. The observation that surface-active agents are cytolytic is not new. Clinical and animal research have confirmed that the toxicity of bile was due to the surface-active bile salts. The effect of surface-active agents on cells was found to be similar to the depolarization of the cell membrane which occurred with injury.[10]

The toxicity of the "spans" and "tweens" was caused by their surface-active properties, but why are they surface-active? Surface activity is imparted by the physical configuration of molecules rather than by any unique chemical properties. The molecule contains a long fat-soluble portion (called non-polar or organophilic, or lipophilic) and a strongly water-soluble portion (called polar or hydrophilic). The fat-soluble portion of the molecule dissolves in a lipid interface and the aqueous-soluble portion tends to pull the lipid into the aqueous phase. Soaps are surface active because the long hydrocarbon chain is lipophilic, and the sodium salt of the carboxy group is hydrophilic. Similarly, glucose monoaleuritate is surface active because glucose is hydrophilic and the hydrocarbon chain of lauric acid is lipophilic.

Since surface activity resides only in the physical configuration of the molecule, it seemed possible to synthesize a water-soluble molecule of long chain length which would supply calories but not be surface active. The most obvious molecule configuration was the dicarboxylic fatty acids. Since these compounds have polar (hydrophilic) groups at both ends of a chain, the chain would not have a fat-soluble and a water-soluble portion, and hence could not orient itself in fatty films as do the surface-active agents.

Verkade[11] believed that fatty acids were primarily metabolized by omega oxidation. He synthesized hexadecanedicarboxylic acid and injected it into the dog to demonstrate that it was metabolized. Although it was metabolized, this did not prove that the C-18 dicarboxylic acid was the important pathway in the metabolism of 18-carbon fatty acids.

Similarly, some of the hydroxylated fatty acids might not form surface-active compounds because the presence of polar groups on the hydrocarbon chain should render their affinity for water greater than for fat. These compounds would lack detergent properties, and should be nontoxic when given intravenously. Since free fatty acids are precipitated by ionic calcium in the blood and may induce hypocalcemic tetany, they cannot be infused. Polyalcohol esters of hydroxylated fatty acids should be water-soluble, nonionic, and if they are nonsurface active they should be nontoxic.

The metabolism of dihydroxy-stearic and tri-hydroxy-stearic acid has been investigated in rats by Harris.[12] These hydroxylated fatty acids aided in the growth and development of rats on diets already presumed to be adequate.

That the hydroxylated fatty acids are metabolized to supply calories is not surprising since a number of such acids have been isolated in substances of animal and plant origin. Acetyl values on human depot fats would indicate that a fair proportion of human depot fat is hydroxylated. In the metabolism of fatty acids, the first step is dehydrogenation with the formation of double bonds. Then there is hydration of the double bond to form a saturated hydroxy fatty acid.[13] This mechanism for oxidation explains the natural occurrence of hydroxylated fatty acids in positions when double bonds are normally found (e.g., aleuritic acid, ricinoleic acid).

In the search for hydrophilic hydroxylated fatty acids several compounds were made including such as tri-hydroxy-, tetrahydroxy-, and hexahydroxy-stearic acids. Of all the hydroxylated fatty acids, the most promising compounds were derivatives of aleuritic acid. Aleuritic acid is a tri-hydroxy-palmitic acid which oc-

curs as a lac secretion from insects, and which constitutes one of the major ingredients of shellac. This fatty acid metabolite can be extracted and crystallized from shellac. The free acid is 0.1 per cent water-soluble. The monoglyceride is 1.3 per cent water-soluble, and the glucose ester is completely water-soluble. The present report deals with metabolic availability and toxicity of one such ester, namely glucose monoaleuritate (GMA).

GMA has a theoretic molecular weight of 467. Because of its large molecular size a 13 per cent solution of GMA is isotonic with 5 per cent glucose, which has molecular weight of 180. One mole of GMA (467 g) requires 54 atoms (864 g) of oxygen for oxidation to CO_2 and H_2O. It would have a theoretic R.Q. of 0.815 which is midway between fat and carbohydrate. One gram of GMA requires 1.85 g of oxygen (1,295 liters) for complete oxidation, and would yield 6.24 cal.

EXPERIMENTAL

Glucose monoaleuritate was synthesized *in vacuo* by transesterifying, in pyridine, ethyl aleuritate with glucose monoacetate. The yields of GMA from free shellac were initially quite low and represented only 15 per cent of the initial starting substance shellac. After purification, bottling, and sterilization, only small amounts were available for animal experimentation.

It was only possible to give substantial quantities of GMA to one animal over a period of 40 days. In another experiment not enumerated here, another animal was given GMA for a 10-day period with a comparable result.

Young growing rats of the Sprague-Dawley strain were used as the experimental animals. The animals weighed between 100 and 150 g.

The rats were weighed each day, and the surface area of each animal was calculated according to a formula described by Lee.[14] The urine of the rats was collected for nitrogen determinations. The rats were kept in an air conditioned room at a temperature of 75° F, although in the fall on several days the temperature fell below the critical temperature and the rats increased their metabolic rates and lost weight on these occasions. This renders the weight-gain curves in the latter part of the experiment slightly irregular. A constant recording thermometer was kept in the animal room to detect these temperature changes. These weight losses can be disregarded since the control animals suffered similar losses, and since there were not many days when the temperature fell below the critical temperature. The food was weighed daily, and the rations were so small in volume that each rat consumed the entire ration offered to him without spillage. The amount of food which was given was calculated from the surface area determinations. In preliminary experiments, it was found that a caloric intake of 1,600 cals/m^2/day was necessary for the maintenance of a satisfactory weight gain under our experimental conditions.

TABLE I

Composition of Two Test Diets

Fat free diet	Composition/100 g	Cal/100 g
Casein	7.50	30
Lactalbumin	5.25	21
Dextrin	55.75	223
Linoleic Acid	0.7	6
Salt Mixture	5.0	—
Liver Concentrate	1.0	—
Vitamins	—	—
Fiber	24.80	—
Total	100.00	280

Control fat diet	Composition/100 g	Cal/100 g
Casein	7.50	30
Lactalbumin	5.25	21
Dextrin	5.75	223
Tripalmitin	13.33	126
Linoleic Acid	0.70	
Salt Mixture	5.00	—
Liver Concentrate	1.00	—
Vitamins	—	—
Fiber	11.47	—
Total	100.00	400

Animals which were used as controls received low-calorie diets prior to the experiment so that their physiologic state would be comparable to that of the experimental group after a similar weight loss. This reduction in weight was accomplished by restriction of the total amount of the standard laboratory food

offered. The control animals were switched to the synthetic diet on the first day of the experiment, and failed to eat and gain for the first few days. Thereafter they took and tolerated the synthetic diet well. The control rats lost approximately 20 per cent of their body weight before starting the experiments.

one diet by the replacement of fat by nonnutritive fiber. The composition of the diets is given in Table I. The animals on the fat-free diet received 1,100 cal/m²/day. One of the three animals given the 1,100 cal diet had a parenteral supplement of GMA equivalent to the amount of purified tripalmitin

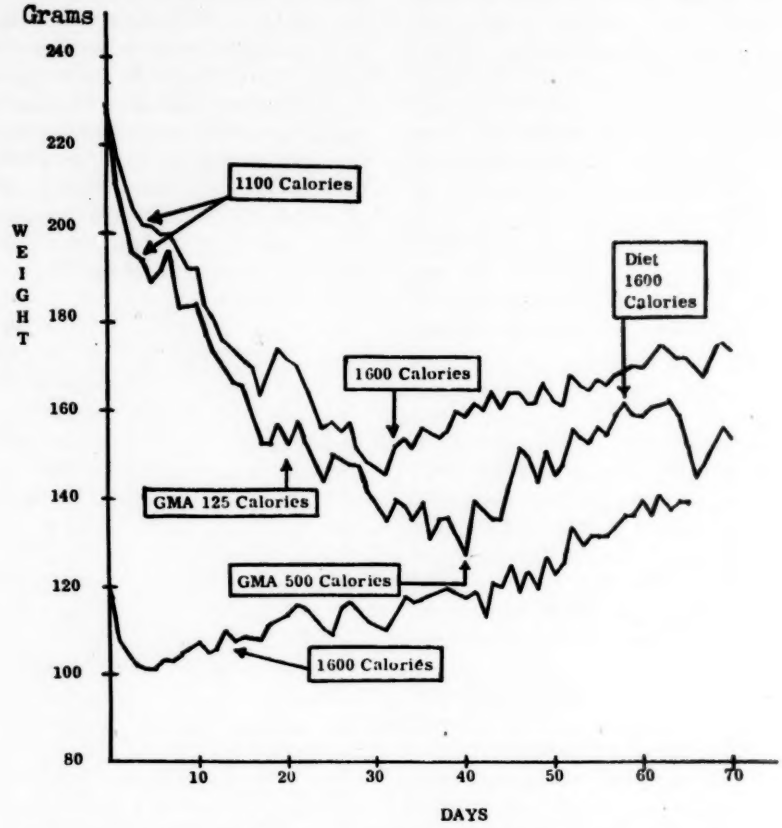

Fig. 1. The weight gains and losses on the diets are indicated. On the twentieth day, 125 cal/m² was given parenterally to a rat on the 1,100 cal diet. The weight loss is retarded but there is no gain until the fortieth day when injected GMA was increased to 500 cal or a total of 1,600 cal. The weight gain at that time paralleled the weight gain of the rats receiving 1,600 cal by diet.

They were then offered 1,600 cal/m²/day by diet. Three rats were used for controls.

The experimental group of three animals received a diet which was identical to the 1,600 cal diet with the exception that it was fat-free. The only difference in the two diets was in their caloric content which was lowered in

in the control diet. In other words, this animal received 1,600 cal/m²/day, of which 500 cal was in the form of parenterally administered GMA. To be sure the effect of GMA was not secondary to its glucose content, one of the three animals on the 1,100 cal diet received an amount of glucose equivalent to that

contained in the 500 cal of GMA. One of the experimental animals was switched to the 1,600 cal diet after a weight loss of sublethal proportions, to make sure that it would gain after the loss. GMA was administered to the experimental animals subcutaneously as a 10 per cent solution. Aliquots of the urine from the animal receiving GMA were taken for glucose and nitrogen determinations. The remainder of the urine was pooled for the 40-day period and extracted and used to quantitatively determine the amount of GMA or free aleuritic acid which might be present.

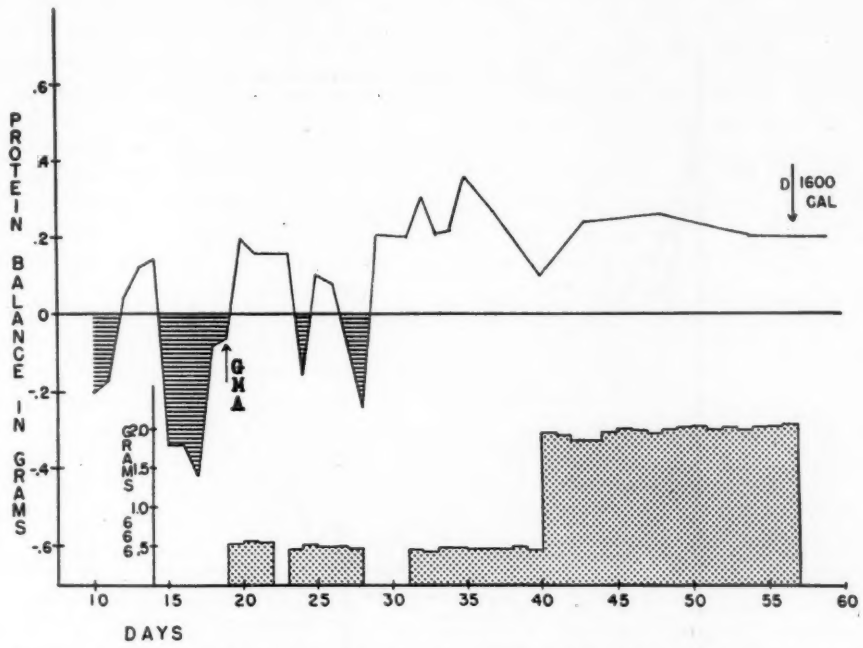

Fig. 2. The nitrogen balance of the animal receiving GMA is indicated. The nitrogen loss was curtailed by injection of 125 cal of GMA but a good positive nitrogen balance was not obtained until 500 cal of GMA was administered.

RESULTS

Figure 1 charts the weights of the animals receiving the fat-free diet. They received 1,100 cal/m²/day. This figure also charts the weights of those rats given 1,600 cal/m²/day. The animals receiving 1,100 cal lost weight at a rapid rate and developed a negative nitrogen balance. The weight decline was almost linear. On the twentieth day, one rat which was receiving the 1,100 cal diet, was given one-fourth of the 500 cal deficit in the form of subcutaneously-injected GMA. In other words, the diet was supplemented with an additional 125 cal/m²/day in the form of parenterally-injected GMA. The weight loss of the rat was curtailed, but he failed to gain. The effect on the nitrogen balance is shown in Figure 2.

On the fortieth day, a total of 1,600 cal/m²/day was given of which 1,100 cal were supplied by the diet and 500 cal by injected GMA. The animal then gained weight at a rate identical to those animals receiving 1,600 cal a day by diet. The final difference between the animals receiving 1,600 cal by diet, and the one animal receiving GMA, is that in one the 500 cal were in the form of GMA, while in the others the 500 cal were in the form of purified tripalmitin in the diet. Parenteral GMA therefore, was as effective in maintain-

ing nitrogen balance and weight gain, as was an isocaloric quantity of dietary tripalmitin. Also, GMA yielded its theoretic number of calories to the rats for metabolic needs. On the sixtieth day of the experiment, the parenterally injected GMA was discontinued and the additional calories were made up in the form of tripalmitin. There was little change in the rate of weight gain. This again shows that GMA was isodynamically equivalent to ingested tripalmitin.

One rat, serving as a control for the 1,100 cal diet, was given the 1,600 cal diet on the thirty-second day after an 83 g weight loss which represented 36 per cent of the initial body weight. The animal responded with a weight gain which paralleled the weight gain of the control-1,600-cal group. The weight gain was also identical to that of the animal which received the parenteral substitute in the form of GMA. This again illustrates the isocaloric equivalence of GMA and tripalmitin by mouth.

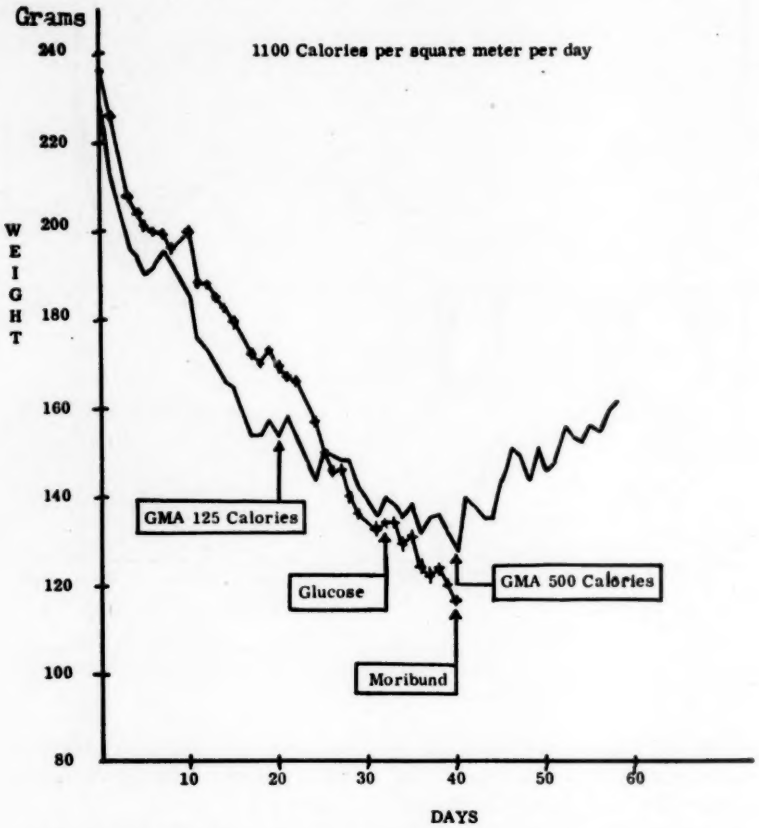

Fig. 3. The animal receiving the 1,100 cal diet was given parenteral injections equal to the amount of glucose contained in GMA. This caloric replacement was unable to prevent fatal starvation. This is not surprising since less than 25 per cent of the calories of GMA are derived from glucose.

In another experiment (Fig. 3), a rat receiving the 1,100 cal/day was given a parenteral substitute equivalent to the amount of glucose which would be contained in the 500 calories of the compound GMA. This small amount of glucose did not influence the weight loss in this animal and indicates that the weight gain

of the animal which received GMA was not secondary to the caloric value of glucose liberated from the rupture of the ester linkage. This small glucose supplement did not prevent a fatal weight loss with the animal being more moribund on the fortieth day of the experiment following a weight loss of 98 g—a total of 42 per cent of the initial body weight. This experiment demonstrates that GMA made possible *survival and even weight gain on an otherwise fatal starvation diet.*

The nitrogen balance of the experimental animal which received GMA is shown in Figure 2. The negative nitrogen balance was ameliorated by partial replacement with GMA but a positive nitrogen balance of a high degree was not established until the animal was given the full caloric replacement with GMA. Animals on a diet of 1,600 cal/m²/day always exhibited a positive protein balance of approximately 0.2 g to 0.4 g per day. Those rats fed 1,100 cal/m²/day showed evidence of a negative nitrogen balance which varied from a positive to a negative balance from day to day, similar to that illustrated in Figure 2. The net effect was a negative protein balance of about 0.2 g per day. Full caloric replacement with GMA produced a positive nitrogen balance which was equivalent to that observed with the control fat diet.

Several days after the conclusion of the experiment, the animal receiving GMA was sacrificed and autopsied. No pathologic abnormalities were found either on gross or microscopic examination of the tissues. The subcutaneous injection site which had been utilized for 40 consecutive days was remarkably free of any inflammatory reaction. During the course of experiments no animal receiving GMA manifested any clinical evidence of toxicity. The material has thus far only been given subcutaneously, in a 10 per cent solution. The injection site exhibits no clinical evidence of inflammatory reaction, and the rats apparently do not experience pain on its injection. An injection in excess of one g has been given at one time, although it was usual to give 0.7 g at each injection. The quantity of GMA injected was usually divided into three doses per day when the rat was receiving full replacement; but on Saturdays and Sundays, the quantity to be injected was divided into two equal doses. No febrile response has been observed after injection of as much as one gram of material. Also, no leukopenia ever developed in several tests made after injection.

After subcutaneous administration of 6 g of GMA, no more than a trace of either it, or aleuritic acid, could be detected in samples of the pooled urines. GMA still retains its reducing properties with respect to Benedict's solution and the other materials which are utilized to test for glucose in urine. It therefore was simple to test the urine for the presence of GMA. No free GMA was found in the urine after as much as the subcutaneous injection of one gram of GMA into a 200-g rat.

The possibility still existed that the glucose was split off and retained by the body and that aleuritic acid was excreted in the urine. This was tested for by alkalinizing the urine and filtering it. Sodium aleuritate is water-soluble. Aleuritic acid can be precipitated by acidifying the alkaline solution: no precipitate developed. Also, the clear urine was tested with calcium chloride. This brings in the precipitation of calcium aleuritate and served as an excellent spot test. No precipitate developed on the addition of calcium chloride.

GMA was non-hemolytic both *in vivo* and *in vitro*. Incubation of blood cells in a 1 per cent solution of GMA buffered at pH 7.3 for one hour at 37° C, induced no hemolysis. The animal which received GMA for a period of over 30 days had a hemoglobin of 15.3 g per 100 ml before administration of the compound, and 15.5 g per 100 ml after administration of GMA. No anemia developed.

DISCUSSION

Parenterally-injected GMA can be isocalorically substituted for dietary tripalmitin with no apparent change in the nitrogen balance and weight gain on an otherwise calorically insufficient diet. The caloric value of GMA is 1.7 times that of glucose, while that of fat is 2.2 times that of glucose. The caloric value

of GMA lies midway between fats and carbohydrates. GMA yields the theoretic number of calories on parenteral injection.

Because of the large molecular size of GMA (molecular weight of 467 as compared to 180 for glucose), high concentrations are not hypertonic as is the case with glucose. For this reason, infusions of high concentrations of material will not cause tissue damage. The fact that GMA is water-soluble makes it possible to utilize avenues of administration other than the intravenous route. We have injected it subcutaneously into rats primarily because we have had difficulty in repeatedly infusing large quantities of material into the tail vein of a rat. The subcutaneous injection of a 10 per cent solution apparently caused no discomfort to the experimental animals. This is important since injection of hypertonic glucose subcutaneously causes considerable local pain.

No toxic symptoms, anemia, or febrile reactions have been observed with GMA as may occur with the administration of fat emulsions. When GMA was the sole source of adequate calories for 40 days without the development of anemia, incubation of human red blood cells with a 1 per cent solution of GMA for one hour did not produce hemolysis. Unlike fat emulsions, GMA is nontoxic, nonhemolytic, produces no febrile reactions.

It is interesting to speculate on the renal handling of GMA. It seems quite likely that the original substance being water-soluble must be filtered. Since it does not appear in the urine, it must be reabsorbed by the tubules. Mannitol and sorbitol are filtered but not reabsorbed. We chose glucose for the esterification because we thought that the glucose moiety might bring about the reabsorption of the entire molecule. This apparently occurred since the free GMA which retains its reducing properties was not present in the urine. Whether GMA enters the cell before the ester linkage is broken or whether part of the ester linkage is split in the blood, is a question that we have not studied but which deserves investigation in the future. We have been able to show that GMA is easily split by esterases in tissue homogenates and blood, but we have not determined the rates at which this transformation occurred.

The fact that a rat could utilize such a large proportion of his caloric requirements in the form of GMA might indicate that GMA is not obligatorily metabolized. Actually, the number of calories supplied by GMA was approximately one-third of the total caloric intake. Ethyl alcohol, which has been used to supply calories, is obligatorily metabolized. Alcohol is immediately metabolized in the body to carbon dioxide and water. Because of this obligatory metabolism, alcohol cannot be converted into fat or carbohydrate for storage. Any energy derived from its metabolism must be obtained immediately. In the case of GMA, one would expect that, since dehydrogenation and hydrogenation can readily occur at the ninth and tenth carbons, the hydroxylated groups in these positions might as well be readily reduced. Omega oxidation has been known to occur, and accounts for approximately 5 to 10 per cent of normal fat metabolism.[15] It is, therefore, possible that a reduction of the omega hydroxylate could also be accomplished by the body. It would be ideal if GMA could enter the normally existent metabolic pools and be called upon when needed, rather than be obligatorily metabolized. This would be possible if GMA could be stored as either the hydroxylated fatty acid (aleuritic acid), or reduced to palmitic acid. It is possible that some storage of the hydroxylated fatty acid itself could occur. Acetyl values of human depot fats indicate that a percentage exists in the form of hydroxylated fatty acids. The question of obligatory metabolism will have to await future definitive studies.

The chief advantage of GMA over the emulsions is that it is water-soluble. Even if one could achieve a stable emulsion of very fine particle size, the intravenous administration of emulsions is fraught with danger from pyrogens and hemolytic anemia. Kuo and Joyner[16] have shown that the infusion of fat emulsions into dogs with experimentally-ligated coronary vessels widens the zone of myocardial ischemia. These authors have also shown that in a number of patients with angina, a fatty meal will induce an attack. Some emul-

sions which are promising with respect to laboratory tests have produced precordial pain when infused into patients.[17] Following hemorrhage, in pernicious anemia, and in other debilitated states leading to tissue-protein depletion, lipemic clearing of the blood is delayed. A lipemia may actually occur in these conditions during the fasting state.[18] It would seem unwise to infuse emulsions into patients who normally have difficulty clearing their blood of endogenously-mobilized fat. Although GMA seems to have many advantages over fat emulsions, all that can be presently stated is that based on our limited experience GMA is non-toxic and non-hemolytic, and can be utilized by the animal to supply the necessary calories for growth, development and the maintenance of nitrogen balance.

It is hoped that glucose monoaleuritate or a closely related substance will fulfill the need for a water-soluble high-energy substance which can be safely administered parenterally to supply calories for patients who are unable to take or assimilate oral nourishment.

SUMMARY

Glucose monoaleuritate is a completely water-soluble ester of aleuritic acid (tri-hydroxy-palmitic acid). The hydroxylated groups on the large carbon chain render it polar, hence the water-soluble ester has no detergent properties. For that reason, it does not cause hemolysis of cells and is non-toxic upon injection into rats. It has a caloric value midway between fat and carbohydrate, but because of its large molecular size, high concentrations of glucose monoaleuritate are not hypertonic. It can be infused without the danger of vascular sclerosis. The parenterally injected material supplies the theoretic number of calories and makes possible growth and development on a diet which would otherwise fail to support life.

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Dietary Survey on Rarotonga, Cook Islands*

II. FOOD CONSUMPTION IN TWO VILLAGES

By PEGGY CROOKE FRY, B.S., M.P.H.†

A PREVIOUS paper described the people on Rarotonga, their living conditions, food habits, and meal patterns.[1] Details regarding the methods of gathering, treating, and analyzing data were also included. The report presently deals with the quantitative dietary findings and the physical measurements of these Maoris.

A total of 308 individuals were studied; 268 native Rarotongans were members of family groups and 40 Maoris were attending a training school for Seventh Day Adventist missionaries in the village of Titikaveka.

DESCRIPTION OF THE SAMPLE

The 268 subjects in 41 families represented 30 per cent of the population of the villages of Titikaveka and Arorangi. There was an age range of from one month through 80 years; yet as can be seen in Table I, it was essentially a young population with 60.9 per cent of the group studied being under 20 years of age and 7.9 per cent over 50 years of age. The occupancy per household averaged 6.5 persons, with 29 (71 per cent) of the families having from five to eight people. The sexes were almost equally represented among the families, there being 137 males and 131 females.

The Titikaveka missionary training school group included 18 girls and 18 boys from 16 to 20 years of age, one girl and one boy 13 years of age, a man and a woman 30 and 40 years of age, respectively. All 40 lived and worked within the limits of the church property on Rarotonga, although many of the students were from outlying islands. The students raised their own food on the church lands with the exception of fish. The only dietary supplements were mangoes and pineapples sent infrequently by the students' parents who lived on other islands, or food purchased with money received from home (which was uncommon as the money usually was spent for clothing or school needs). This missionary school survey was made during the hurricane season, thus the receipt of mail from home was negligible, since very few ships arrived during this time.

TABLE I

Rarotongan Population, Showing Age Groups

	Total island population* (N = 6048) %	Family survey population (N = 268) %	N
Under 1 yr	3.6	3.4	9
1–3 yr	26.4	29.1	26
4–6 yr			32
7–9 yr			20
10–12 yr	26.4	28.4	25
13–15 yr			26
16–20 yr			25
20–30 yr	14.8	13.4	36
30–40 yr	11.2	10.1	27
40–50 yr	7.6	7.8	21
50–70 yr	8.6	6.0	16
70–90 yr	1.3	1.9	5
Total			268

* From *Official Census of 1951.* Rarotonga. Analysis of age groups—natives. Registrar's Office, Rarotonga, Cook Islands. Unpublished.

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METHODS

The methods for calculating the average family nutrient intakes and obtaining the nutrient allowances for each family have been described previously.[1] The average daily intake of nutrients was derived by dividing each family's total intake by the number of days it was studied. The family survey findings are presented in two forms. It is hoped that in this way they may be of more value for comparative purposes in other similar investigations.

The first method follows Bigwood,[2] who has suggested the use of coefficients of consump-

TABLE II

Coefficients of Consumption

Age	Cal	Prot.	Ca	Fe	A	Thia.	Ribo.	Nia.	Asc. acid
Birth to 1 yr	0.4	0.5	1.0	0.5	0.3	0.3	0.4	0.3	0.4
1–3 yr	0.4	0.6	1.3	0.6	0.4	0.4	0.6	0.4	0.5
4–6 yr	0.5	0.8	1.3	0.7	0.5	0.5	0.8	0.5	0.7
7–9 yr	0.6	0.9	1.3	0.8	0.7	0.6	0.9	0.6	0.8
10–12 yr, male	0.8	1.1	1.5	1.0	0.9	0.8	1.1	0.8	1.0
10–12 yr, female	0.8	1.1	1.5	1.0	0.9	0.8	1.1	0.8	1.0
13–15 yr, male	1.0	1.3	1.8	1.3	1.0	1.0	1.3	1.0	1.2
13–15 yr, female	0.8	1.2	1.6	1.3	1.0	0.8	1.3	0.8	1.1
16–20 yr, male	1.1	1.5	1.8	1.3	1.0	1.2	1.6	1.2	1.3
16–20 yr, female	0.8	1.2	1.6	1.3	1.0	0.8	1.2	0.8	1.1
20+ yr, moderately active male	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
20+ yr, moderately active female	0.8	0.85	1.0	1.0	1.0	0.8	0.9	0.8	0.9
Pregnant female, last trimester	0.9	1.2	1.9	1.3	1.2	0.9	1.3	0.9	1.3
lactating female	1.1	1.5	2.5	1.3	1.6	0.9	1.6	0.9	2.0

TABLE III

An Example of the First Method of Calculating Nutrient Intake (Iron)

Age groups	Population proportions	N. R. C. recommendations* *mg*	Column 1 × column 2	Number in the group	Coefficient of consumption	"Consumption people"
1–3 mo	0.0112	6	0.0672	3		
4–9 mo	0.0037	6	0.0222	1	0.5	4.5
10–12 mo	0.0187	6	0.1122	5		
1–3 yr	0.0970	7	0.6790	26	0.6	15.6
4–6 yr	0.1194	8	0.9552	32	0.7	22.4
7–9 yr	0.0746	10	0.7460	20	0.8	16.0
Males						
10–12 yr	0.0373	12	0.4476	10	1.0	10.0
13–15 yr	0.0410	15	0.6150	11	1.3	14.3
16–20 yr	0.0336	15	0.5040	9	1.3	11.7
Adults	0.2090	12	2.5080	56	1.0	56.0
Females						
10–12 yr	0.0560	12	0.6720	15	1.0	15.0
13–15 yr	0.0560	15	0.8400	15	1.3	19.5
16–20 yr	0.0597	15	0.8955	16	1.3	20.8
Adults	0.1530	12	1.8360	41	1.0	41.0
Pregnant, last trimester	0.0075	15	0.1125	2	1.3	2.6
Lactating	0.0224	15	0.3360	6	1.3	7.8
Total	1.0000		11.3484†	268		257.2‡

* N. R. C. = National Research Council.

† 11.3484 = the weighted value of daily iron needs per composite Rarotongan.

‡ 257.2 = the total number of "consumption people" for the mineral, iron.

TABLE IV

Nutrient Intakes Obtained by the First Method

Nutrients	Total no. of "consumption people" 1	Mean no. of consumption units/family 2	Total of families' average daily intake 3	Average daily intake/consumption unit* 4	Daily need of composite Rarotongan 5	Percentage intake of daily need 6
Calories	208.5	5.1	744,465.9	3,571.0	2,220.0	161
Protein (g)	253.9	6.2	24,887.6	98.0	62.0	158
Calcium (mg)	337.7	8.2	103,866.0	307.6	1,005.0	31
Iron (mg)	257.2	6.3	4,680.2	18.2	11.4	160
Vitamin A (I.U.)	221.6	5.4	3,118,128.6	14,071.0	4,142.0	340
Thiamin (mg)	202.9	5.0	384.5	1.9	1.2	158
Riboflavin (mg)	257.8	6.3	281.8	1.1	1.5	73
Niacin (mg)	202.9	5.0	3,482.3	17.2	11.9	145
Ascorbic acid (mg)	239.1	5.8	37,219.6	156.0	67.0	233

* Column 4 is derived by dividing Column 3 by Column 1.

TABLE V

Comparison of Actual and Recommended Intakes for the Families

Nutrients	Ratings						Range %	Mean %	Standard deviation %
	Poor (<75%)		Fair (75–100%)		Good (100%+)				
	No. of families	%	No. of families	%	No. of families	%			
Calories	0	0	6	15	35	85	83–304	130	± 37.45
Protein	1	2	6	15	34	83	67–512	161	± 79.23
Calcium	39	95	2	5	0	0	20–99	40	± 15.49
Iron	0	0	4	10	37	90	91–924	169	±131.36
Vitamin A	15	37	0	0	26	63	6–1,452	262	±282.99
Thiamine	5	12	9	22	27	66	62–340	127	± 51.56
Riboflavin	26	63	8	20	7	17	31–218	72	± 34.09
Niacin	8	19	11	27	22	54	35–323	115	± 55.04
Ascorbic acid	6	15	3	7	32	78	11–535	210	±129.69

tion as a means of deriving individual nutrient intakes from the family intake; therefore calculations of consumption coefficients were made, based on the caloric needs and the current recommendations of the National Research Council for other nutrients. The new coefficients are presented in Table II. Multiplying the number of people in the different age groups by the coefficients of consumption and adding up the column for each nutrient produced the total number of "consumption people" for each nutrient. By dividing the total number of "consumption people" for each of the nutrients into the total average daily nutrient intakes of the 41 families, the average daily intake of each nutrient per consumption unit was derived. In order to have a standard for comparison, weighted values of the recommended needs of the composite Rarotongan were calculated again, using the age profile of the 41 families, and the recommendations of the National Research Council[3] and the Food and Agriculture Organization.[4] Table III is an example of these computations for iron, while the results for all nutrients are summarized in Table IV.

The second method of presenting the nutrient intakes is as a percentage of the recommended intakes for each family.[5] The homes were divided into three groups with respect to each of the nutrients: those consuming more than 100 per cent of the recommendations ("good"); those with intakes between 75 and 100 per cent ("fair"); and those with less than 75 per cent ("poor"). The results of this arbitrary division of percentages are seen in Table V, and the same material is presented graphically in Figure 1.

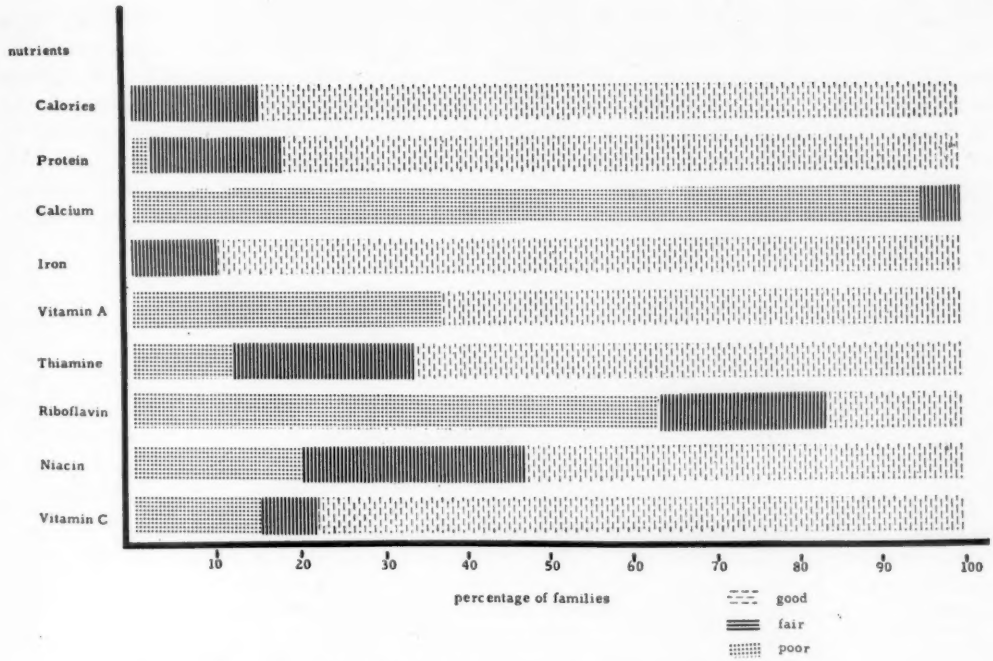

Fig. 1. Percentage of families classified with respect to quality of nutrient intakes.

TABLE VI

Range of Adequacy of Nutrient Intakes, Based on the First Method

Nutrients	Low (family no. 18)		High (family no. 32)	
	Coefficients of consumption	Average intake/ day/consumption unit	Coefficients of consumption	Average intake/ day/consumption unit
Calories	5.60	2,291.00	4.40	5,536.20
Protein (g)	6.70	73.70	5.85	188.30
Calcium (mg)	8.90	170.30	7.80	435.90
Iron (mg)	6.90	11.60	6.00	35.80
Vitamin A (I.U.)	6.00	15,024.00	5.00	5,747.20
Thiamine (mg)	5.50	1.04	4.40	2.75
Riboflavin (mg)	6.70	0.82	6.00	1.65
Niacin (mg)	5.50	13.02	4.40	29.59
Ascorbic acid (mg)	6.40	67.30	5.50	259.00

RESULTS

Comparison of Intakes and Allowances

Two of the families in the survey serve to illustrate the range in adequacy of intake, based on coefficients of consumption. Family No. 18 was composed of an 80-year-old female, a man and wife both 35 years of age, and four children, one eight-year-old girl and three boys 15, 13, and 1 years of age. Family No. 32 contained six persons, three males 20, 5, and 4 years of age and three females 79, 19, and 14 years of age. The differences in intake of these families are great, as evidenced in Table VI. In both instances, the adults of the households were engaged in agriculture; no one worked for a weekly cash income.

Application of the second method of presenting nutrient intakes showed that there was

no family in either the "poor" or "good" group with respect to all nine nutrients. Thirty-five (85 per cent) of the 41 families had "good" intakes of four or more nutrients, while five (12 per cent) had "poor" intakes of four or more nutrients. No family was rated "poor" in calories or iron, nor was any family "good" in calcium intake.

neither better nor worse nutritionally than those who did have a weekly cash income.

When the data were analyzed to determine the influence of family size on dietary status, it was seen that the 14 families with five or fewer members averaged 2.86 ± 1.18 nutrients in the "poor" or "fair" categories, whereas the other 27 families with six or more members

TABLE VII

Nutrient Composition of the "Typical" Daily Family Diet

Food	Average consumption/family g/day	cal	Prot. g	Fat g	CHO g	Ca mg	Fe mg	Vitamin A I.U.	Thiamine mg	Riboflavin mg	Niacin mg	Ascorbic acid mg
Pacific Island biscuits	26	93.	2.6	0.7	19.	5.	0.4	—	0.02	0.03	0.4	—
Bread	1,535	3,914.	115.1	4.6	841.	353.	15.4	—	1.54	—	—	—
Flour	68	239.	6.8	0.7	51.	11.	1.4	—	0.04	0.03	0.7	—
Rice	18	63.	1.3	0.2	14.	1.	0.1	—	0.01	0.01	0.2	—
Doughnuts	69	278.	4.4	15.2	31.	35.	0.9	154.	0.15	0.12	—	—
Bananas	402	323.	3.1	0.9	75.	22.	1.6	1,098.*	0.16	0.19	1.6	31.
Breadfruit	1,293	1,409.	19.4	3.9	323.	323.	12.9	453.*	2.59	—	—	194.
Sweet potatoes	906	932.	15.4	7.7	200.	154.	5.4	23,103.*	0.82	0.45	5.4	154.
Tapioca	441	491.	2.7	—	120.	93.	3.8	—	0.09	0.40	—	113.
Taro	1,058	772.	18.9	—	175.	219.	8.8	351.*	0.44	0.54	3.5	—
Taratarua	289	289.	5.8	—	66.	72.	2.9	116.*	0.15	0.15	2.0	29.
Non-fatty fish	1,648	1,615.	313.1	41.2	—	330.	16.5	—	0.99	2.47	49.4	—
Molluscs	42	27.	6.1	0.3	—	2.	1.3	—	0.01	0.05	0.6	—
Fresh pork	95	410.	7.8	42.1	—	9.	1.4	—	0.81	0.22	3.9	—
Fresh chicken	67	62.	8.5	3.2	—	7.	1.3	—	0.07	0.07	2.7	—
Canned beef	398	971.	99.5	63.7	—	72.	15.9	119.	0.04	0.80	10.0	—
Powdered, whole milk	22	107.	5.6	5.9	8.	198.	0.2	308.	0.07	0.25	0.2	1.
Butter	25	186.	0.1	20.6	—	4.	0.1	675.	—	—	—	—
Fat	45	401.	—	44.6	—	—	0.1	—	—	—	—	—
Coconut cream	1,393	4,680.	41.8	473.6	70.	209.	13.9	—	1.25	—	—	—
Tahitian chestnuts	159	267.	4.3	2.4	66.	45.	1.8	—	0.33	0.27	0.6	38.
Avocados	61	89.	0.9	8.5	2.	4.	0.4	85.*	0.04	0.06	0.4	9.
Oranges	270	87.	1.6	—	20.	61.	0.6	506.*	0.16	0.05	0.4	91.
Rukau (*taro* leaves)	100	29.	4.1	0.5	2.	107.	1.3	20,000.*	0.15	0.47	1.6	43.
White sugar	106	424.	—	—	106.	—	—	—	—	—	—	—
Cocao powder	8	34.	1.6	2.0	2.	4.	1.1	12.*	0.01	0.02	0.1	—
Tea leaves	21	9.	2.2	—	3.	28.	—	—	—	0.05	6.5	—
Coffee, ground	16	7.	0.7	—	1.	9.	—	—	—	0.02	2.1	—
Average intake/day/family		18,208.	693.4	742.5	2,195.	2,377.	109.5	46,980.	9.94	6.72	92.3	703.
Average recommended intake/day/family		14,529.	404.0	—	—	6,539.	74.0	28,281.	7.70	10.00	77.0	442.
Per cent of recommended intake		125.	171.6	—	—	36.	147.9	166.	129.	67.	119.9	159.

* I.U. vitamin A in the foods as carotene. Carotene values converted to I.U. of vitamin A by dividing the totals by 3 and adding that number to the totals of vitamin A values.

Eleven of the families had one member who worked for a weekly cash income. These 11 households had an average of 3.36 ± 1.67 of the nine nutrients classified as "poor" or "fair," while the remaining 30 families averaged 3.73 ± 1.49 nutrients in these groups. Student's "t" test was applied and the differences were not found to be statistically significant. The families having no wage earner were

produced a mean of 4.04 ± 1.54 nutrients in these groups. Student's "t" test indicated that the difference between the groups was significant at the 2 per cent level. It seemed, therefore, that the smaller the family, the better the dietary status.

The total amounts of the foods listed by 15 per cent or more of the families[1] (Table I) were averaged in terms of daily quantity per

family, using 41 as the constant denominator. The nutritive values of the "typical" diet are found in Table VII. The average daily recommendations per family are given for purposes of comparison; Table VII indicates the more important sources of the nutrients and is an aid in understanding the results presented previously in other tables.

fats, and carbohydrates was calculated for each family, as was the amount of animal protein in the total protein intake; conversion factors of 4, 9, and 4 cal/g respectively, were used in determining the average values given in Table IX. This table compares the surveys of the family group and of the Seventh Day Adventist group. This distribution approx-

TABLE VIII

Nutrient Intake of Missionary Training School Students

Nutrients	Method no. 1					Method no. 2	
	"Consumption people"	Average intake/day	Average intake/consumption unit	Daily need of composite student	Per cent intake of need/day	Per cent of recommended allowance	Rating
Calories	42.35	82,843.5	1,956.2	2,877.9	68.0	72	Poor
Protein (g)	52.95	1,478.0	27.9	85.9	32.5	43	Poor
Calcium (mg)	66.60	14,233.1	213.7	1,323.0	16.4	27	Poor
Iron (mg)	51.40	534.8	10.4	14.9	69.8	90	Fair
Vitamin A (I.U.)	40.00	1,792,221.8	44,805.5	5,000.0	89.6	90	Fair
Thiamine (mg)	39.60	46.7	1.2	1.5	80.0	76	Fair
Riboflavin (mg)	54.90	38.5	0.7	2.2	31.8	45	Poor
Niacin (mg)	39.60	377.0	9.5	15.4	61.7	61	Poor
Ascorbic acid (mg)	47.40	8,077.8	170.4	88.9	191.7	227	Good

The dietary intake of the people living in the Seventh Day Adventist mission is summarized in Table VIII. Both methods of deriving individual intakes from the group intake were applied. It should be emphasized that (a) fewer subjects were studied here than in the family survey, hence the differences in adequacy of intake may be exaggerated by the smallness of the sample; (b) attempting to counter-balance the first factor, records were kept for the missionary students for ten days, rather than the more usual seven; and (c) all the food preparation and cooking at the training college was done in one place for consumption by the entire group. No bread, tea, coffee, sugar, milk, or meat (other than fish) was listed during the ten days, inasmuch as these are foodstuffs which would have to be purchased and the students had no funds to do so; moreover, the consumption of tea and coffee is prohibited by the religion of these students. Some raw fresh fruits such as papayas, ripe bananas, or mangoes might have been consumed and been omitted from the records.

The caloric distribution between proteins,

TABLE IX

Percentage of Calories Derived from Carbohydrate, Fat, and Protein

Components	Per cent of total calories	
	Family survey	Training school survey
Carbohydrates	49.4 ± 11.0	49.5
Fat	37.8 ± 10.4	42.3
Total protein	12.8 ± 3.4	8.3
Animal protein	53.4 ± 15.2	12.1
Plant protein	46.6 ± 12.6	87.9

imates that reported by Phipard[6] on American family food supplies. The term "animal protein" is used here to include protein derived from beef, pork, chicken, and milk powder as well as fish and shellfish. Thirty-two (78 per cent) of the families consumed animal protein in quantities of 40 per cent or more of the total protein.

Physical Measurements

Standard adjustable bath scales measuring to the nearest pound were used to obtain the weights of 265 subjects (117 males and 148 females). Care was taken to place the scales

on a flat, hard surface in order to obtain as much accuracy as possible. Since light cotton dresses for the females and tropical-weight shorts for the males were the usual attire, no allowance was made for clothing. Shoes were not worn during any of the measurements.

pometer was lowered until it rested on the scalp. A reading was taken to the nearest millimeter.

In Table X average heights and weights are given for both sexes, while Figures 2 and 3 compare Rarotongans with another Polynesian group, the Tongans.[7] The average

TABLE X

Weights and Heights of Rarotongans

Age group (in years)	Weight, lb			Height, cm		
	No.	Mean	Range	No.	Mean	Range
			Females			
Under 1 yr	2	14.5	12–17	—	—	—
1–2	6	24.7	21–28	2	79.95	77.3– 82.6
2–4	12	34.1	21–44	8	99.66	79.8–112.7
5–7	12	46.5	32–68	12	111.63	99.0–124.3
8–10	12	59.2	42–84	12	124.56	108.5–142.4
11–13	14	87.0	57–127	14	144.84	124.7–159.5
14–16	11	120.9	70–150	11	157.84	137.0–172.1
17–19	31	167.9	103–182	31	159.25	135.1–170.8
20–24	9	149.1	132–174	9	161.88	153.4–169.2
25–29	8	148.6	97–202	8	162.84	153.7–167.9
30–34	4	176.8	123–222	4	158.48	151.0–163.5
35–39	5	146.2	99–188	5	160.24	151.7–165.2
40–44	8	155.0	128–212	8	158.16	150.2–162.4
45–49	5	150.2	116–181	5	158.94	156.9–162.1
50+	9	151.9	117–168	9	155.82	151.5–159.2
Total	148			138		
			Males			
Under 1 yr	2	18.5	16–21	—	—	—
1–2	7	21.4	12–32	3	72.96	66.8– 82.7
2–4	15	36.3	28–44	12	97.72	91.2–108.6
5–7	13	50.9	42–64	13	114.66	104.1–124.0
8–10	9	61.1	46–76	9	127.89	122.0–139.3
11–13	10	86.3	66–114	10	146.05	134.0–157.0
14–16	8	116.3	89–150	8	160.63	146.7–175.9
17–19	10	143.8	122–166	10	167.95	160.3–176.9
20–24	12	151.5	103–190	12	165.47	158.2–168.4
25–29	5	142.0	120–164	5	166.94	160.6–180.5
30–34	6	172.3	127–218	5	166.38	160.0–175.1
35–39	7	184.3	148–216	7	174.50	169.2–183.5
40–44	4	197.3	133–280	4	169.13	163.4–177.0
45–49	3	165.3	145–187	3	170.97	164.0–177.7
50+	6	160.8	134–174	6	170.05	167.9–172.1
Total	117			107		

Stature was measured on 245 Rarotongans (107 males and 138 females). Subjects were asked to stand with arms held loosely at their sides, looking straight ahead, heels together, and toes pointed slightly outward. While in this posture, with buttocks and heels lightly touching a wall, the sliding arm of an anthro-

weight and height of all Maori female subjects over 20 years of age was: 154.0 lb ± 9.2 lb (70.0 kg) and 159.5 cm. ± 2.2 cm. (62.8 in). The same data on all measured Rarotongan males over 20 years of age were: 167.6 lb ± 17.6 lb (76.2 kg) and 169.1 cm ± 3.1 cm (66.6 in). The growth of Maori children

from birth to seven years of age is reported on in a separate paper.[1a]

A thorough search of the literature failed to produce any data on mean weights-for-age of Americans from birth to 60 years of age. Therefore, material from four sources[8,9,10,11] was obtained to produce the comparative data for American males and females seen in Figures 2 and 3. The literature revealed *no* information on age changes in adult stature for Americans of both sexes.

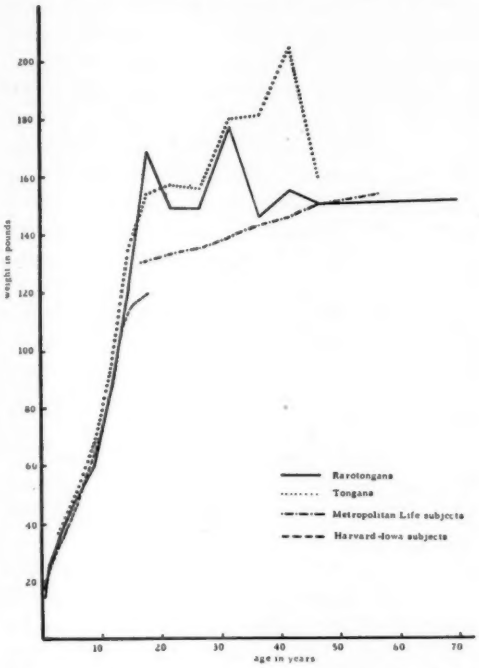

Fig. 2. A comparison of weight according to age among female Rarotongans, Tongans, and Americans.

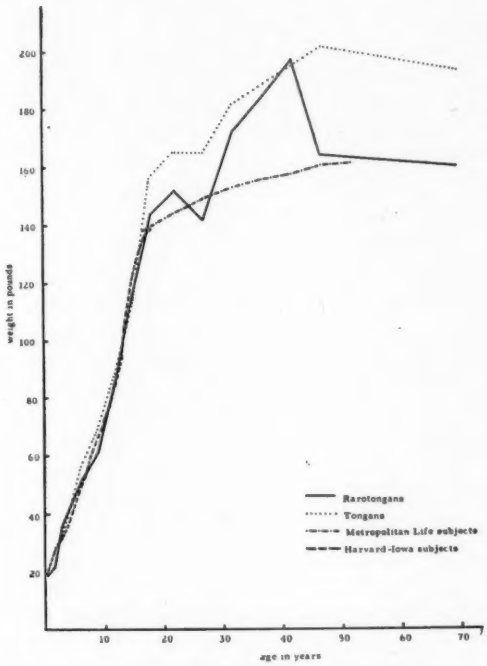

Fig. 3. A comparison of weight according to age among male Rarotongans, Tongans, and Americans.

DISCUSSION

Calcium and riboflavin, in that order, were the nutrients consumed in the most inadequate amounts. Thirty-nine (95 per cent) and 26 (63 per cent) of the families, respectively, were considered "poor" in these nutrients (Table V). The heads and small bones of fish are routinely consumed along with most of the internal organs, and it appears that calcium intake may have been underestimated on these grounds. However, some overestimation may have been made since *taro* roots and leaves and *maniota* roots are known to contain substantial amounts of calcium oxalate salts[12] so that thorough cooking is necessary to prevent the needle-like crystals in these foods from irritating the digestive tract.

Miller[13] has reported that the availability of calcium from these sources is quite doubtful in view of the large quantities of oxalic acid free to combine with the mineral, although Potgieter[14] has stated that the calcium of *taro*, eaten in the form of *poi* (an Hawaiian *taro* dish), was well utilized by human beings. The large consumption of sweet potatoes, breadfruit, and *taro* gives these foods an important place as possible contributors of both calcium and riboflavin to the Rarotongan diet. Chemical analyses and vitamin assays by Miller[15] have shown that these foods furnish far more of the B-vitamins and calcium than do white flour and white rice. Increased consumption of milk, and green, leafy vegatables would appear to be the best way to

insure a more adequate intake of calcium and riboflavin.

There are plant leaves other than those of the *taro* plant which are used in times of food scarcity. For example, the leaves of the cassava and sweet potato plants are rich in calcium, riboflavin, carotene, and ascorbic acid.[16] More extensive use of these leaves should be encouraged. Langley[17] reported that Fijians used certain ferns and bush plants (*Hibiscus* and *Solanum* species) as well as *taro* leaves; these same plants have been identified on Rarotonga[18] and could be utilized for food there as well, if their value was shown to the Maoris.

The introduction of some pulses or legumes to Rarotonga seems a most advisable measure; education of the people to know the value of these and how to grow and prepare them for consumption would be extremely important in the success of such a venture. Mung and goa beans, pigeon and cow peas, peanuts, and soya beans have all been grown to some extent on Pacific islands of volcanic origin. It is, therefore, feasible to try growing them on Rarotonga where they can be depended upon to raise the B-complex vitamins and calcium contents of the diets as well as to increase the vegetable protein and iron elements of the diets.

Recommending consumption of fresh milk would be an ill-advised measure under present conditions of an exceedingly small supply, with no pasteurization procedures in practice. Increased importation of skimmed milk powder with a decrease in the selling price and a subsidy paid to storekeepers if necessary, in conjunction with a nutrition education program is an alternate possibility.

Caloric recommendations were more than met by quantities of starchy roots and fruits and coconuts. Fish provided the largest single source of protein and niacin, as well as contributing substantially to the riboflavin, iron, and calcium intakes.

Although there was no one food rich in iron, the intake was greatly above the usual recommendations, as seen in Tables IV and V. These findings should be considered in the light of the reports from Faine and Hercus[19,20] regarding intestinal parasites. Their 1950 survey revealed that beyond one year of age ". . . 87 to 100 per cent of the population (average 88 per cent) had ova present, throughout the various age groups." The ova found were of the types: *Ascaris*, *Trichuris*, Hookworm, and *Enterobius;* the technic used limited investigation for the presence of other parasites. It is remarkable that this high degree of parasitization seemed to have left so small a mark on the general health of the people. The same authors report that although infestation with intestinal helminthiases was common, the results of hemoglobin determinations and of erythrocyte counts showed no signs of iron deficiency, and no serious anemia, even among women of reproductive age. No blood tests were made in conjunction with the present dietary survey. However, there have been no improvements with regard to excreta disposal since the Faine and Hercus survey, and their findings undoubtedly still hold true.

As is seen in Table V, there is a tremendous range in the intake of vitamin A and ascorbic acid; this is in accord with the report of Young[21] that in northeastern United States subjects, vitamin A and ascorbic acid are the most variable nutrients. The most important source quantitatively, of carotene for the Rarotongans is root vegetables, and in particular sweet potatoes. *Taro* leaves are rich in carotene with 20,000 I.U. per 100 g edible portion, and greater use of these leaves would be beneficial to the people. The internal organs of fish, pork, and chicken supply an unmeasured amount of vitamin A to the Rarotongan diet.

Examination of the daily intake of the "typical" family in Table VII shows that carotene is the source for 97 per cent of the vitamin A in the diet. This is a disproportionate amount of carotene, and the efficiency of absorption and conversion of these precursors to vitamin A becomes of great importance. It may be inappropriate to use one I.U. of vitamin A as the equivalent of three I.U. of carotene under these circumstances; but this ratio was used by Buchanan[16] as well as in Table VII. During the summer or hurricane months on Rarotonga, there was a noticeable

increase in the incidence of tropical cutaneous ulcers. Charters[22] has rather conclusively ascribed the causation of *ulcus tropicum* to deficiencies in vitamin A and calcium. These are the same months of the year when food shortages are most likely to occur.

Although there was low consumption of fresh fruits and green vegetables, the ascorbic acid intake seemed good. Starchy roots and fruits contributed virtually all of this nutrient to the dietary. These foods are all subjected to cooking, including bananas when used in the green, unripe state. Some preparation loss did occur, but the methods used were conservative and should not have caused excessive destruction, since steaming in the earth oven was the method most commonly used.

Miller[23] has reported that mangoes, papayas, and guavas are good to excellent sources of carotene and ascorbic acid, the range in vitamin A values being from 2,500 to over 5,000 I.U. in every 100 g of edible fruit and the ascorbic acid varying from 30 to over 60 mg per 100 g of edible portion in these three tropical fruits. She has found, further, that the calcium content of certain Pacific fruits was surprisingly high: tamarinds had the highest calcium content (0.113 per cent) reported in the literature for any fruit and were equal to some vegetables in this respect. Oranges are superior to most other fruits in calcium content; most of the mineral is in the membrane, and consumption of this along with the juice, as is frequently done on Rarotonga, yields over 0.02 g calcium per 100 g of edible fruit. Guavas, which are extremely common on Rarotonga, are a fair source of calcium as well (0.01–0.02 g per 100 g of edible fruit).

A daily intake of more raw indigenous fruits by all age groups would provide a better safeguard against deficiencies in this labile vitamin.

Traditional native foods—coconut cream, starchy roots and fruits, fish and *rukau*—were the principal contributors of the B vitamins. White bread and the occasional consumption of roast pork supplemented the usual intake of thiamine niacin and, to a lesser extent, riboflavin.

It can be seen by a comparison of Tables V and VII that there was not a proportionate distribution of the food supply among the families. Only to a limited extent are the Maoris continuing the old traditions of communal living. Had there been more equal distribution of the foodstuffs, there would have been no families classified as "poor" for any of the nutrients except calcium and riboflavin, and these only because the majority of families were deficient in these two nutrients.

Some trends could be seen in the habits of the Maoris in times of food shortages. The supply of fish within the lagoon has been decreasing as a consequence of the lack of regulations concerning the minimum gauge of netting to be allowed for fishing. The netting in use allows the very smallest fish to be caught, thus preventing their growth to the reproductive stage.

There are about seven canoe passages in the fringing coral reef surrounding Rarotonga, through which small canoes or boats may go at low tide in order to fish in the open sea. Within the families studied in the villages of Titikaveka and Arorangi, a relationship existed between the distance each family lived from one of the few reef openings and the amount of fish that was listed for them, those closest to the reef passages ate more fish. Attempts by the New Zealand government to dynamite new boat passages through the reef have been unsuccessful so far.

Among the families who: (a) lived some distance from the reef openings, and (b) lacked an adult male to go fishing and do the heavy work of *taro* cultivation, there was an increased consumption of *kumara* (sweet potatoes), and breadfruit, when it was in season. Sweet potatoes mature four to six months after planting and require little cultivation. A breadfruit tree begins to bear fruit five to seven years after planting, and seems to require no special care.

Small octopus and bêche-de-mer, because they can be caught within the lagoon by females, become the principal protein sources for those few families who come close to semistarvation. Families living under such circumstances were found to differ from the overall "typical" household by consuming less total protein and less riboflavin but having a more satisfactory

intake of ascorbic acid and calcium (sea slugs contain 120 mg calcium per 100 g edible portion) and a very high carotene intake (sweet potato carotene content varies with the variety from 4,000 to 7,000 I.U. per 100 g edible portion). Nine varieties of sweet potatoes were identified on Rarotonga by Wilder.[18]

Faine and Hercus[19] mention the increasing dependence of Rarotongans on imported foodstuffs, mainly tinned meat, sugar, flour, and tea. These foods unquestionably do have prestige value, and their continued use by individuals living in a subsistence economy is a cause for some concern. The very few cows, goats, pigs, and chickens that were kept were in obviously poor condition and there were no attempts being made at scientific animal husbandry. That the traditional native foods were still important contributors to the average Maori diet can be clearly seen by close examination of Table VII; fish, coconuts, and the six starchy roots and fruits provided from 54 to 74 per cent of all the nine nutrients calculated in the typical family dietary.

The missionary training school of 40 persons had five nutrients in the "poor" group and only one considered "good" (Table VIII). There is sufficient evidence, if the recommendations used as a standard approximated the real needs of the group, that these people are being inadequately fed. All nutrients except iron, vitamin A, and ascorbic acid need to be substantially increased in their daily intakes. The trainees routinely had only two meals a day (at noon and in the evening), with little opportunity to purchase store foods. The limited variety of dishes is indicated by the small number (ten) of food items recorded for the group during the ten-day survey period. Sufficient time and encouragement are given to gardening, but more guidance and nutrition education are necessary, particularly concerning the cultivation of green leafy vegetables. The religion of these people prevents food preparation, cooking, or cultivation on Saturday, which necessitates the gathering and preparing of enough food on Friday to last until Sunday noon.

It would seem advisable to have more time expended for fishing or gathering of shellfish and sea slugs. There appeared to be an almost adequate consumption of the high carbohydrate staples; if these foods were supplemented with more fish, shellfish, and dark green leaves, the quality of the diet would be greatly improved in all respects. The value of the liberal use of dark green leaves must be demonstrated to the Rarotongans. Calcium and riboflavin would be the nutrients most difficult to increase above 75 per cent of the recommended amounts. Increased consumption of shellfish, fish, and bêche-de-mer would be a valuable addition to the calcium as well as riboflavin and protein content of the mission members' diets. Before increased fishing is encouraged, regulations and plans should be made concerning the minimum size fish to be caught and retained, and the re-stocking of the lagoon.

It was not feasible to conduct reliable activity studies on the Rarotongans. From observations, it is believed that day-to-day living involves sufficient hardships so that the calorie requirements should be reduced with age by less than the 7.5 per cent for each decade beyond 25 years, which the Committee on Calorie Requirements[4] recommends. In the case of the mission students, the activity level is perhaps a bit lower than that of their counterparts within the families, since they are engaged in classroom activities for approximately six hours a day, five days a week. People of the same ages within the family groups are usually occupied with tasks related to cultivation of the staple foods or cash crops, fishing, gathering wood and water, and other household duties.

The Tongan study[7] had a very small sample size (38 males and 88 females over 20 years of age), as did the present survey (42 males and 48 females over 20 years of age). As a result, wide fluctuations are evident in Figures 2 and 3, making it difficult to see definite trends in weight changes with increasing age in Polynesians.

Comparison of the average adult Rarotongans at all ages above 20 years with the average Americans and Tongans of the same age showed the large weight differences were present; the average Tongan woman was

heavier than the Rarotongan female by 19 lb and Maori women averaged 10 lb heavier than United States women. The Maori men had a mean weight exceeding their American counterparts by 12 lb and the Tongan males were heavier than the Rarotongan men by an average of 16 lb.

If obesity is a problem in the United States, it would appear to be an even greater one in these two Polynesian groups. The term obesity is used here as meaning "an excessive accumulation of fat in the body,"[24] a rather vague but frequently-used definition. A particularly pertinent fact here is that body weight alone is an inadequate estimate of degree of fat accumulation, since total weight also takes into account body organs and fluids, hard tissues and muscle mass.

It is believed by the author and E. I. Fry[25] that the muscular development of Rarotongans is superior to that of Americans, and that this tendency continues from childhood until approximately 40 years of age. The exigencies of living do not permit the Rarotongans to depend on labor-saving mechanical devices for their food, clothing, and shelter. Until they have reached a relative old-age status and have older children to assist in the daily tasks, these people must work hard to earn the necessities of life, thus developing this superiority in musculature.

At approximately 40 years of age women begin to discontinue their part in the more arduous tasks of food production, and to spend more time in rather sedentary tasks within the home. It seemed that male Rarotongans generally decreased their energy expenditures at nearly the same age as did the women, though to a smaller degree. The latter still were performing the tasks of plowing, planting, harvesting, and fishing, but there was usually more help available to them at that age. This decrease in physical exertion is not always accompanied by a reduction of caloric intake, so that the gradual replacement of muscle by adipose tissue which normally takes place with decreased exercise may occur simultaneously with added fat deposition due to overeating. The importance of heredity cannot be overlooked in the production of such muscular types of people; through the years, natural selection has probably occurred in favor of mesomorphy.

The life expectancy of Maoris is much different from that of Americans; as can be seen in Table I, relatively few Rarotongans live beyond 40 years of age though to what extent this may be due to dietary habits rather than types and prevalence of diseases and inadequate sanitation and hygiene cannot be stated at the present time. Extremely slender and exceedingly obese adults are to be found on Rarotonga, as in most other areas of the world. However, should a campaign aimed at weight reduction be launched, it would constitute a social as well as a dietary problem. In Rarotongan culture, fatness is desirable in women and is associated with respect and social prestige in men. It is not realized by the Maoris that concomitant with obesity go increased risks of developing certain degenerative conditions, such as cardio-vascular-renal diseases and diabetes. Whether or not this is true among Polynesians cannot be determined until more data are available on the incidence of these diseases among them.

Little significance can be attached to the findings on stature measurements. One reason for this is that there is such a dearth of research data available on changes in height with age beyond 20 years, in any racial group, Americans not excepted. When all the adults of the two Polynesian groups were compared with each other, it was found that the Tongans exceeded the Rarotongans, the average Tongan male being 5.1 cm taller and the average Tongan female being 2.8 cm taller than the average Rarotongan man and woman.

An evaluation of the weight and height tables and of previous reports[19,20] would seem to indicate that the Rarotongans, as a whole, were not in a poor nutritional state, despite their seemingly serious deficiencies of calcium and riboflavin. Too little is known of human needs for these two nutrients and of the factors causing variations in the efficiency of utilization by different races.

SUMMARY

A dietary survey of 308 Polynesians was made on Rarotonga, Cook Islands. Forty-one

families contained 268 of the subjects and the remaining 40 people were students in a missionary training school. There were six villages on the island and the number of individuals studied represented 30 per cent of the population of the two villages in which they lived. It is believed that the present report indicates the long-term average nutrient intakes of the Rarotongans today.

The evidence presented showed that 60 to 95 per cent of the families consumed less than 75 per cent of the National Research Council's recommended intakes of calcium and riboflavin, and one-third of the families were in the same low category for vitamin A. The mission students were found to be consuming less than 75 per cent of the amounts of calories, protein, iron, riboflavin, and niacin that were recommended for them. The intakes of all other calculated nutrients seemed more satisfactory for both groups.

It was found that families having no wage earner were neither better nor worse nutritionally than were the families who did have a weekly cash income. Family size influenced the dietary status of the households, i.e., the smaller the family the better its dietary rating.

Weight measurements indicated that obesity (or overweight) may be a problem on Rarotonga; however, there are grounds for believing that exceptional muscularity rather than excessive adiposity accounted for much of the heaviness encountered in adult Rarotongans.

There has been insufficient study of physiologic requirements under tropical conditions of poor sanitation, where there is an increased need for high resistance to diseases of parasitic and infectious origins. In addition, too little is known about the nutrient composition and biologic availability of food stuffs commonly consumed by Maoris. For these reasons, it is important that the comparisons made between nutrient intakes and standards be regarded as tentative. The adequacy of a diet is determined in the final analysis by the health of the population consuming it, and it can be said, on the basis of the present report, that within their short life spans, Rarotongans do not show overt signs of suffering from widespread malnutrition.

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Obesity and Hypertension Among Young Adults

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THE present paper deals with the results of investigations regarding the incidence of obesity and hypertension and their possible correlations among 3,508 University of Chicago students (registered in 1954). The relation of hypertension to race, climate, age, and environment among students was analyzed in a previous study.[1]

SCOPE AND MATERIAL

All cases of obesity which were considered endogenous, i.e., all cases of hormonal dysfunction (dystrophia adiposogenitalis, etc.), were excluded from the study and so were all cases of secondary (non-essential) hypertension. No one with any evidence of heart disease, kidney ailment, or hormonal dysfunction (diabetes, hyperthyroidism, etc.) was included.

The blood pressure, body weight, and height were determined at the time of the entrance examination. The student was usually recalled for re-examination of the blood pressure when it was found to be elevated at the first examination. The height (in centimeters) and weight (in kilograms) were determined without shoes and (in men) without coats. The blood pressure was considered elevated if it was 140/90 mm of mercury or above. This limit was chosen because it is the most generally accepted.[1] The reasons for the selection of this criterion have been presented elsewhere.[1]

To determine the "normal" weight, Broca's formula was used, i.e., normal weight in kilograms equals the number of centimeters of the height above 100. This formula, introduced into clinical investigation by Moritz in 1908, seems to be the simplest and most useful method. According to Glatzel[2] the values yielded by this method are useful in the age group above 35 to 40, but for younger people the values are somewhat too high.

TABLE I

Association between Obesity and Hypertension

	Hypertensive	Normotensive	Total
Obese	111	868	979
Non-obese	125	2,404	2,529
Total	236	3,272	3,508

In spite of the fact that people of different types of body build (asthenic, sthenic, or hypersthenic) have a different "normal" weight, it appears to be a safe assumption that any one with a weight in excess of that given by Broca's formula is "overweight." It is particularly true in our cases since the subjects for this study consisted of an overwhelming majority of young adults, the great majority of whom were under 30 years of age. On account of this age distribution the criteria for obesity can be made more strict than would have been possible in a survey of the general population including all age groups or the older age groups.

The criteria of obesity used in this study certainly will not include any one with a normal or subnormal weight, but may exclude a few individuals who may be considered slightly overweight by other methods, although the correspondence by this method with standard tables is quite good. For example, by Broca's method a man 6 feet (183 cm) tall is considered to have a normal weight of below 183 lb (83 kg without coat and shoes), whereas according to the commonly used Metropolitan

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Life Insurance Company "ideal weight" table[3] a man six feet tall should weigh from 152 to 185 lb (69 to 84 kg), "as ordinarily dressed with shoes." It should also be noted that although the term "obesity" is used here, the data do not exclude subjects who may be "overweight" because of an exceptionally developed muscle mass.

RESULTS

Data on obesity and hypertension among the students examined are presented in Table I. According to the criteria mentioned there were 236 hypertensive and 979 obese subjects in a total population of 3,508 students. These groups comprise 6.7 and 27.9 per cent, respectively, of the entire student sample. Among these 236 hypertensives, one hundred and eleven or 47 per cent are obese. Among the 3,272 normotensives eight hundred and sixty-eight or 26.5 per cent are obese. The incidence of obesity differs markedly between the hypertensive and normotensive groups.

Analyzing the data according to sex and birthplace (geographic origin) it appears (Table II) that 29 per cent of the young male population and 23.9 per cent of the female population is obese. There was no significant difference in the incidence of obesity among the American and among the foreign-born students.

From Table II it is quite clear, however that there is a significant difference regarding hypertension between American and foreign born. This is more striking if one analyzes the number of hypertensive subjects among non-obese students; 6.3 per cent of the American males and 2.7 per cent of the foreign-born males, 1.5 per cent of the American females and 3.7 per cent of the foreign-born females being hypertensive. No other significant difference was encountered between American and foreign-born students according to Table II.

The incidence of hypertension among non-obese American males is four times higher than among the American female students. The same is true, to a somewhat lesser degree, of the total population; however, there is no significant difference in incidence between the sexes among the foreign born.

Highly significant in the total population examined is the difference in the incidence of obesity among *normotensive* and *hypertensive* students, the ratio being 26.5 per cent to 47 per cent, respectively. Still bigger is the difference if one analyzes the occurrence of hypertension among the non-obese and obese population. Only 4.9 per cent of the non-obese students are hypertensive, but the percentage of hypertension more than doubles to 11.3 per cent among the obese.

TABLE II

Association between Obesity and Hypertension among American and Foreign-Born Males and Females

	No. of students examined	Obese in the total population		Obese among the non-hypertensive (normotensive)		Obese among the hypertensive		Hypertensive in total population		Hypertensive among non-obese		Hypertensive among obese	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
American													
Male	2,366	691	29.2	605	27.8	86	44.5	193	8.1	107	6.3	86	12.4
Female	690	168	24.3	154	22.7	14	63.6	22	3.1	8	1.5	14	8.3
Total	3,056	859	28.1	759	26.7	100	46.5	215	7.0	115	5.2	100	11.6
Foreign born													
Male	349	98	28.0	88	26.5	10	58.8	17	4.9	7	2.7	10	10.2
Female	103	22	21.1	21	21.2	1	25.0	4	3.8	3	3.7	1	4.5
Total	452	120	26.5	109	25.2	11	52.3	21	4.6	10	3.0	11	9.1
All male	2,715	789	29.0	693	27.6	96	45.7	210	7.7	114	5.9	96	12.1
All female	793	190	23.9	175	22.8	15	57.6	26	3.2	11	1.8	15	7.8
Total	3,508	979	27.9	868*	26.5	111*	47.0	236	6.7	125*	4.9	111*	11.3

* The difference is highly significant ($P < 0.01$).

In this study, the incidence of obesity in the male population is higher than among females. It seems that younger women in a college student group are more apt to keep their weight down than do young men.

There are almost twice as many hypertensive American males (12.4 per cent) among the obese as among the non-obese (6.3 per cent). The incidence of hypertension among the young American obese males is higher by one third than among females.

The distribution of obesity according to age groups is approximately the same among the normotensive and hypertensive students. No significant difference was found on comparing the different age groups in respect to obesity and hypertension. While there is a slow increase in the rate of hypertension among the obese with increasing age, the difference is not very significant. In the age group over 40, 22.5 per cent of the obese are hypertensive; however, the small number of persons (forty) included in this age group does not permit the drawing of definite statistical conclusions. It was not possible to establish a definite tendency to develop hypertension with increasing age among the younger obese subjects.

Obesity seems to increase among the foreign born with increasing number of years spent in the United States. According to Table III 25.4 per cent of 208 foreign-born students who have spent less than one year in the United States were obese. One hundred and fifty foreign born have spent one to ten years in the United States; 26.6 per cent of them were obese. Finally, 28.7 per cent of the 94 foreign born who have resided longer than ten years in the United States were obese or "overweight."

TABLE III

Obesity among Foreign Born According to the Years Spent in America

	Total	Less than 1 yr		1–10 yr		More than 10 yr	
		No.	%	No.	%	No.	%
All foreign born	452	208	46	150	33.2	94	20.7
Obese foreign born	120	53	44.1	40	33.3	27	22.5
Percentage of obesity in year groups		25.4%		26.6%		28.7%	

TABLE IV

Incidence of Hypertension and Obesity According to Race and Sex

American born	No. of students	Obese		Hypertensive		Foreign born	No. of students	Obese		Hypertensive	
		No.	%	No.	%			No.	%	No.	%
White						European					
Male	2,297	668	29.0	184	8.0	Male	186	68	36.5	13	6.9
Female	652	160	23.1	21	3.2	Female	60	14	23.3	4	6.6
						White					
Negro						Non-European					
Male	51	18	35.1	8	15.6	Male	62	14	22.5	2	3.2
Female	31	7	22.5	1	3.2	Female	17	5	29.4	0	0
Oriental						Asiatic					
Male	16	3	17.7	1	6.2	Male	92	14	15.2	1	1
Female	6	1	16.6	0	0	Female	23	2	8.6	0	0
American Indian						African					
Male	2	2	100.0	0	0	Male	7	1	14.2	1	14.2
Female	1	0	0	0	0	Female	1	1	100.0	0	0
						South American					
						Negro					
						Male	2	1	50.0	0	0
						Female	2	0	0	0	0

The incidence of obesity and hypertension according to race and sex among the American and foreign-born students is presented in Table IV.

It would be important to learn the incidence and the relation between obesity and hypertension in different racial groups who are living in the same environment. Unfortunately the figures presented in Table IV are not large enough to permit definite conclusions regarding this question.

TABLE V

Diastolic Pressure Values among Subjects with Systolic Pressures above 140 mm

Diastolic pressures	Below 80 mm		80–89 mm		90–99 mm		100 or more mm		
	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	Total
American									
Male	20	39	33	35	21	28	12	5	193
Female	1	0	5	5	6	2	3	0	22
Foreign born									
Male	1	4	5	3	2	0	1	1	17
Female	0	0	0	2	1	1	0	0	4
Total									
Male	21	43	38	38	23	28	13	6	210
Female	1	0	5	7	7	3	3	0	26
Total	22	43	43	45	30	31	16	6	236

Although the criterion of hypertension was set at 140 mm systolic pressure (see above) it is of interest to examine the distribution of diastolic pressures among obese and non-obese subjects. These data are presented in Table V. In addition it should be pointed out that there were 25 obese subjects with a diastolic pressure above 90 mm, but with a systolic pressure below 140 mm. In this study they were included as normotensives. This group consisted of 20 American males and 3 females plus 2 foreign-born males. Table VI presents additional observations on the distribution of hypertensives (divided now on the basis of diastolic pressure) among the obese.

TABLE VI

Subjects with Systolic Pressures *above* 140 mm

	Diastolic pressure below 90 mm	Diastolic pressure above 90 mm	Total
Obese	65 (58.6%)	46 (41.4%)	111
Non-obese	88 (70.4%)	37 (29.6%)	125
Total	153 (64.9%)	83 (35.1%)	236

DISCUSSION

The importance of obesity and hypertension, their influence on degenerative diseases, and effect on longevity have been emphasized by many authors. The remark of Rynearson and Gastineau[4] is quite correct: "it is easy to shrug off 'a few pounds overweight' as something of little consequence, but in so doing, the physician is ignoring what is perhaps his best chance to lengthen the life and diminish the future illness of his patient." According to Master and Jaffe[5] the death rate in obese men runs as much as 60 per cent above normal.

Levy, and associates[6] found that "transient hypertension, transient tachycardia or overweight, each by itself, increases the probability of the later development of sustained hypertension and of cardiovascular-renal disease. The presence of two of these conditions is of greater importance, in this respect, than any one alone."

According to Master *et al.*[7] "among the (hypertensive) men overweight was decidedly more frequent than it was among the general population, the ratio being 32.2 per cent to 14.8 per cent." They did not find "significant differences in the frequency of obesity among the hypertensive women and the control group." In this present study the corresponding percentages were even higher and the difference was highly significant both in the male and female population.

Moschowitz[8] found that "even in individuals within the range of normal weight, the blood pressure is in general proportionate to weight."

Davies (quoted by Schroeder[9]) found that hypertension is almost twice as frequently associated with obesity among men and women in a hospital population as would be expected by the incidence of each one alone. It is significant that in this study which deals *not* with a hospital population, but with healthy and young people, the findings bear out this statement—the corresponding figures being 26.5 per cent obese among the normotensives and 47 per cent among the hypertensives; 4.9 per cent hypertensives among the non-obese, but 11.3 per cent among the obese.

Short and Johnson[10] examined 2,858 healthy individuals and found that overweight exerts a positive influence in causing increased incidence of hypertension, but in their study the incidence of hypertension in the overweight group was generally lower than reported by other observers.

The importance of obesity is again emphasized by the fact that more than 20 per cent of the population of the United States is overweight according to recent government reports.[11]

SUMMARY

Using 140 mm Hg systolic blood pressure limit as a criterion for hypertension, and the Broca formula as the criterion for obesity in a young adult population (3,508 college students) it was found that the difference in the incidence of obesity between the normotensive and hypertensive students was statistically highly significant (26.5 per cent of the normotensives and 47 per cent of the hypertensives were obese).

The incidence of hypertension was 8.1 per cent among the American and 4.9 per cent among the foreign-born *males*. It was found that 979 or 27.9 per cent of the students (29 per cent of the males and 23.9 per cent of the females) were overweight. The incidence of hypertension was 4.9 per cent and 11.3 per cent, respectively, among the non-obese and the obese students. The difference is highly significant, there being more than twice as many hypertensives among the obese as among the non-obese. Of the obese 12.4 per cent and of the non-obese 6.3 per cent of the American males were hypertensive.

No significant difference was found in the different age groups in respect to hypertension and obesity. No increase in the incidence of hypertensive obesity was found with increasing age below the age of forty. The incidence of obesity gradually increased among foreign-born students with increasing number of years of American residency.

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Population Studies on Serum Cholesterol and Dietary Fat in Yugoslavia

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POPULATION differences in regard to serum cholesterol are considered important from the point of view of public health.[1] While the level of serum cholesterol can not serve as a reliable criterion of blood vessel integrity in individuals[2] (cf. 2), it was found useful as an index of the so-called atherogenic potential in population studies.[3] The observed differences in cholesterol have been related to the fat content of the diet but previous population studies concentrated on the amount rather than the kind of fat.[4]

The principal aim of this study was to examine the relative effects on serum cholesterol of different dietary fats in populations sharply differentiated in their fat consumption. Opportunities for such a field study presented themselves in the fall of 1953 in Croatia, with its marked contrasts between the various areas: the fertile, corn and hog-raising Northeastern area; (the "animal fat" region); the Adriatic islands where the climate is ideally fitted for growing olive trees but little else except some vegetables, fruit (figs and grapes), and nuts (almonds); the "olive oil" region, and the barren mountain area off the Adriatic coast, which until very recently was economically underdeveloped, its agriculture unproductive and which was characterized by a low intake of all kinds of fat.

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Qualitatively, the contrast between the "animal fat" region near the Hungarian border and the "olive oil" island region is very clear and definite, and attention will be focused principally on the comparison of these two areas.

DIET

The three dietary regions were selected on the basis of information available at the Division of Food and Nutrition, Central Institute of Hygiene, Zagreb, supplemented by the preliminary results of a food consumption survey organized by Ferber in 1952[5] and by contacts with the local public health authorities.

The town of Dalj, near Osijek, served as a prototype of settlements in the "animal fat" area. The villages of Boraje, Lepenica and Vrsno in the Dalmatian Hinterlands, some 20 miles East of Sibenik, are located in the "low-fat" region. Sali, on Long Island (Dugi Otok), was considered a good representative of the "olive oil" area.

Even though substantial variations are present within each region, Ferber's study[5] contains data useful for the characterization of the animal-fat and low-fat areas. In 1952 in the Osijek (animal-fat) region the average daily per capita caloric intake was 2,763 cal as contrasted with the value of 1,952 cal for Dalmatia's low-fat area. This difference is reflected in the adult body weight, as will be shown in the anthropometric description of the subjects.

The total protein intake in these two areas was 97 and 69 g per day, with a still more striking contrast in animal protein (52 vs. 19 g). The reported carbohydrate intake was

similar, with 352 and 343 g per day while consumption of milk (307 vs. 98 ml/day), fresh meat (100 vs. 20 g /day), and fat (98 vs. 26 g/day) differed markedly.

In the Osijek (animal-fat) region a substantial amount of fat is consumed in the form of smoked bacon, fat pork meat, ham, and dairy products while the use of vegetable oils is negligible. In the selected locality (Dalj) the consumption of pork, meat, and lard is very high in comparison with either the Dalmatian Hinterlands (low-fat area) or Long Island (olive-oil area). In the region of continental (low-fat) Dalmatia in which the field work was done the dietary picture was somewhat complicated by the recent opportunities for some of the peasants to work on factory construction at Ražine near the coast. This provided additional income enabling a limited number of families to raise somewhat their standard of living. Both lard and some olive oil were used in this area.

Sali, on Long Island, representative of the "olive-oil" region, is a farming-fishing community. "Farming" involves growing grapes and vegetables, (including a spinach-like plant called *blitva*, available in abundance late into the fall), and the care of extensive groves of olive trees. Fish is an important source of fresh meat. According to information obtained in interviews with the men in our sample group, olive oil represented about 90 to 95 per cent of all fat that is used as such in the household. On the basis of a limited survey of 14 households, selected at random, the average per capita intake of olive oil was estimated at about 85 g/day.

In the majority of households olive oil is the only visible fat used. It is highly appreciated and is plentiful, except following olive-crop failures. In some households animal fat is used for a short time around Christmas when a lean hog is butchered. Our field work was carried on during October.

The concrete information available for the specific localities in which the investigations were made was, in itself, limited. However, the differences in the agricultural practices and the dietary aspects of the mode of life in the "animal-fat" and "olive-oil" areas are very striking and are probably as large as can be found between any two regions inhabited by peasants of the same national stock. The total fat intake in the "animal-fat" and "olive-oil" regions was very similar, representing about 30 per cent of the total calories in both regions. The fat in the "low-fat" region represented about one third to maximally one half of that consumed in the other two areas.

SELECTION OF SUBJECTS

An effort was made to obtain random samples of the subjects within each decade and area. In Sali (olive-oil area) and Boraje with its neighboring villages (low-fat area) the population census of 1953, in Dalj (animal-fat area) the list of voters was used as the basis. Names were then obtained taking every second, third, fourth man, according to the number of individuals engaged in agricultural work in each decade, until 25 to 30 names were obtained. These men received an invitation, using local administrative channels, to avail themselves of a special medical examination. The yield varied somewhat but approximated about 90 per cent, on the average. It was highest on the island ("olive-oil" area), where the ground work was prepared most adequately by prior correspondence and meetings with the town administration and invited influential citizens. It was lowest in the mountainous "low-fat" area. Unfortunately, hemolysis of some of the samples reduced the number of individuals for whom the cholesterol content of the blood could be determined.

For the sake of good public relations a few additional men not qualified either on account of age or occupational activity were examined. Their data were not considered here. A few individuals with infectious disease (tuberculosis) or fever were examined clinically but were not measured and were excluded from the sample.

METHODS

Body Measurements

The body measurements included in this study serve to characterize (1) size and bulk

(weight) of the body, (2) bony framework, (3) relative underweight-overweight and (4) leanness-fatness. Height, weight, bicristal diameter (as a measure of the bony width of the pelvic girdle), upper arm circumference, and the skinfolds at the back of the upper arm (over the triceps) and below the right scapula were measured in accordance with the preliminary recommendations of the Committee on Nutritional Anthropometry.[6] In addition, the width of the limb bones was characterized in terms of the epicondylar diameters of the humerus and femur. Chest circumference was measured at the level of the mammae, at the end of normal expiration. The level of the "waist" circumference was defined as midway between the top of the iliac crest and the ribs, along the midaxillary line. The "waist" skinfold was measured at the intersection of the waist circumference and the midaxillary line. Ventral skinfold was measured on the upper arm (over the biceps) at the level of the upper arm circumference.

Blood pressure was determined with a pressure cuff, calibrated against standard pressures.

Serum Cholesterol Determinations

Determination of cholesterol in blood was performed by a modification of the method of Bloor.[7] In this method there is no saponification and the results are somewhat higher than those obtained by the method of Abell *et al.*,[8] which is currently used in this Laboratory. The samples taken at the place of investigation were centrifuged and sent to the chemical laboratory in Zagreb. During transportation the samples were kept on ice. The maximum time before the analysis was eight days. Lipids were extracted from the serum using Bloor's mixture. The solvent was evaporated and the color was developed using Liebermann-Burchard reagent at 22° C and read at 625 mμ in the Beckman spectrophotometer.

Statistical Analysis

Standard methods of analysis were utilized for examining the relationship between age and cholesterol in each dietary region, and the differences between the regions.[10,11] The tests, in the form of appropriate F ratios, concern (1) the presence of significant linear age trends; (2) significance of deviations from linearity; (3) difference between slopes obtained for cholesterol in the three regions; (4) significance of the distance between the regression lines, provided the slopes are not significantly different.

CHARACTERISTICS OF THE SUBJECTS

The number of subjects in each decade and dietary region, for whom valid cholesterol determinations are available, is given in Table I. The mean ages within each decade are very similar and would allow a direct comparison of mean values of serum cholesterol.

TABLE I

Number and Mean Age of Subjects for Each Decade and Region

Diet	Age, decades: Third	Fourth	Fifth	Sixth	Total
	Size of the sample (N)				
Animal fat	21	17	25	16	79
Low fat	9	14	23	18	64
Olive oil	17	21	18	10	66
	Mean age				
Animal fat	24.7	33.7	43.7	53.6	39.0
Low fat	24.8	33.9	43.4	54.2	41.7
Olive oil	24.5	33.3	43.7	53.1	36.9

In respect to height, all three regions showed the usual trend toward lower values at higher ages but the decrements became marked only in the sixth decade. More interesting is the absence of substantial increments with age in body weight. As a consequence, the American weight standards appear to provide valid comparison for young men but not for the subsequent decades. Under these conditions it may be useful to use as a reference the ratio of weight to height based on grand means for the combined samples (N = 209) and compute the relative values of the weight-height index for each decade within the three regions. This was done in Table II.

Men from the "low-fat" area are clearly lighter no matter which criterion is used. The

TABLE II

Anthropometric Characteristics: Height (cm), Weight (kg), Relative Weight (Actual as Percentage of U. S. 1912 Standards), and Relative Weight/Height Index.

Diet	Age, decades Third	Fourth	Fifth	Sixth	Total
	Height, cm.				
Animal fat	168.7	172.1	168.3	166.8	168.9
Low fat	173.3	169.3	171.9	166.0	169.9
Olive oil	173.4	172.3	173.7	169.5	172.5
	Weight, kg				
Animal fat	66.1	67.8	67.4	65.2	66.7
Low fat	64.0	64.1	63.5	60.7	62.9
Olive oil	68.1	70.0	70.0	69.5	69.5
	Relative weight (% of U. S. 1912 standards)				
Animal fat	102.2	97.4	97.8	94.8	98.1
Low fat	94.3	95.1	88.8	89.0	90.5
Olive oil	100.4	100.5	94.8	98.2	98.6
	Relative weight/height index				
Animal fat	99.1	99.8	101.5	99.0	100.0
Low fat	95.0	95.9	93.6	92.6	94.3
Olive oil	99.5	102.9	102.1	103.9	102.1

TABLE III

Serum cholesterol, mg/100 ml, means (M) and standard deviations (SD).

Diet		Age, decades Third	Fourth	Fifth	Sixth	Total
Animal fat	M	223.6	240.6	235.7	258.1	238.1
	SD	40.4	50.5	45.6	56.9	
Low fat	M	197.4	211.2	211.0	227.5	213.8
	SD	27.9	32.5	37.4	28.4	
Olive oil	M	170.5	207.7	212.3	198.4	198.0
	SD	24.0	35.0	56.4	30.2	

TABLE IV

Age trends in serum cholesterol. Statistical tests of the presence of a significant linear trend and of the departure from linearity.

Diet	F-test Linear trend	F-test Departure from linearity
Animal fat	3.814†	0.533
Low fat	3.997*	0.836
Olive oil	6.370††	2.609

* Significant at 5% level.
† Approaches the 5% level of significance.
†† Significant at 1% level.

other two regions are similar to each other in weight, the "olive-oil" region exhibiting slightly higher mean values. Skinfolds, as more direct measures of leanness-fatness, are thickest in the "animal-fat" area but the difference between this and the "olive-oil" region are small. The subjects from the "low-fat" area are thinnest and the values of their circumferences and bony dimensions suggest a less robust body build. In terms of the bicristal diameter/height index subjects from the "animal-fat" region are somewhat more "stocky", with a mean of 17.6 as compared with 17.2 for the other two regions. This mean difference is small but it is statistically significant.* Regional differences in blood pressure are also small, with a suggestion of higher values in the "animal-fat" area.

RESULTS

Means and standard deviations of serum cholesterol for each decade and dietary region are given in Table III. Throughout, the means are highest for the "animal-fat" and lowest for the "olive oil" region, with the low-fat region being intermediary. The only case of overlap is at the fifth decade where the mean of the "olive-oil" group is somewhat higher than that of the "low-fat" group. While within each decade the mean ages are very similar (see Table I), the number of individuals in each decade varies. As a consequence, the mean ages for the three regions differ and the grand means for cholesterol (Table III) are not directly comparable.

In order to combine the data for all the age groups and to test statistically the significance between regions, a combination of regression analysis and analysis of variance was used. In all three regions a linear age trend is present which closely approaches or exceeds the five per cent level of statistical significance (left column in Table IV). Further analysis is substantially simplified by the fact that the age trends do not depart significantly from linearity (right column in Table IV).

Regression equations for cholesterol and age

* $F = 14.62$ (for 1 and 143 degrees of freedom, $F_{0.01} = 6.82$).

are given in Table V (left column). At a constant age of 40 years, which is close to the mean age of the three regional samples, there is a difference of 38 mg/100 ml between the results obtained from the "animal-fat" and "olive-oil" regions.

No significant differences were observed between the rates of increase in cholesterol with age (Table VI, left column). Consequently it is legitimate to use a common slope (Table VII). The difference between the cholesterol levels adjusted for age is about the same as when separate slopes for the two areas were used, i.e., 38 mg/100 ml. Statistically the differences between the levels of the regression lines are significant in the comparisons of "animal-fat" vs. "olive-oil" and "animal-fat" vs. "low-fat" areas (Table VI, right column).

TABLE V

Regression equations for serum cholesterol ($\hat{Y}$) and age (X, in years)

Diet	$\hat{Y} = a + bX$	$\hat{Y}$ for X = 40
Animal fat	200.489 + 0.972X	239.4
Low fat	180.581 + 0.795X	212.4
Olive oil	152.518 + 1.233X	201.8

TABLE VI

Differences between dietary regions in regard to the slope (b), and the level of regression lines (intercept, a, with a single common slope).

Diet	Difference between slopes, F_b	Difference between levels, F_a
Animal fat vs. Olive oil	0.135	26.435*
Animal fat vs. Low fat	0.070	14.730*
Low fat vs. Olive oil	0.410	2.287

* Significant at 1% level.

TABLE VII

Regression equations for serum cholesterol ($\hat{Y}$) and age (X, in years), using a common slope (b_c)

Diet	$\hat{Y} = a + b_cX$	$\hat{Y}$ for X = 40
Animal fat	198.221 + 1.030X	239.4
Low fat	170.751 + 1.030X	212.0
Olive oil	159.974 + 1.030X	201.2

DISCUSSION

It is now well established that variations in the proportion of calories contributed by fats tend to be reflected directly in the mean serum cholesterol concentration of many populations: peoples whose diets are low in fats tend to have lower serum cholesterol values than do peoples whose diets are high in fats. Similarly, when persons in a "high-fat" country such as the United States go on a low-fat diet, the serum cholesterol tends to fall and to stay low if the low-fat diet is continued. But these facts have to do, in general, with differences in the amounts and not in the kinds of fats in the diet. On the whole, populations consuming high-fat diets are very prosperous and their diets are high in fat because they can indulge in the more expensive foods of animal origin, and the "richest" parts of those foods (e.g., cream, butter, well-fattened meats). When such people are forced to go on a low-fat diet, either because of economic change or on medical advice, they reduce the fat in the diet by cutting down the obviously fat, "luxury" foods. Conversely, when a poor population subsisting on a cheap low-fat diet becomes more prosperous, one of the first results is a change to a diet containing more of the luxury foods, i.e., more fat meats and dairy products.

In all of these circumstances a proportionality between total fats and serum cholesterol tends to prevail. A high-fat diet in which animal fats represent only a small part of the total fats is a rare situation among populations though it is readily contrived in experiments. Experiments on man with such diets have shown considerable differences between the cholesterogenic effects of different dietary fats. With almost equal amounts of fats in the experimental diets, Groen and others[12] observed lower serum cholesterol values when their subjects were on vegetarian diets than on ordinary mixed diets. Kinsell and others reported a lowering of the serum cholesterol when hospitalized patients were fed on a synthetic diet containing large amounts of cottonseed and soy oil[13,14–16]. In this Laboratory, Keys and Anderson carried out two six-month experiments on 23 and 26 men respectively and found significantly lower cholesterol values

with cottonseed oil than with butterfat in the diet, even though calories, proteins, total fats and dietary cholesterol were constant. At 36 to 37 per cent of total calories from all fats and three-fourths of the fat being either butterfat or cottonseed oil, the mean serum cholesterol value for 26 men was 240.7 (±8.0) mg per 100 ml on butterfat and 195.9 (± 6.7) on cottonseed oil. Finally, it was observed that lower serum cholesterol averages were found for men in Naples, whose diets averaged 20 per cent of total calories, than for men in dietary experiments in Minnesota on diets equivalent in total fats.[17]

This was the background for the present study. Since it was completed there have been several reports indicating that the proportion of saturated to unsaturated fatty acids in the dietary fats may be a major determinant of the cholesterogenic effect.[18–21] Many animal fats, including butterfat and probably the fats of all common meat animals (but not of fish), are relatively saturated. Vegetable fats run all the way from very saturated (coconut oil) to relatively unsaturated. Olive oil is moderately unsaturated, with an iodine number of 79–88.

The present results are, of course, compatible with the theory that the relative saturation of the fatty acids is important in fixing the serum cholesterol level. Undoubtedly, the mean saturation of the fatty acids in the diet of the people in the "animal fat" region was considerably greater than fats in the diet in the "low-fat" region, but uncertainties on this point, as well as the complications introduced by different calorie intakes, make deductions from the "low-fat" region hazardous.

SUMMARY

Serum cholesterol was determined in clinically healthy subjects in three localities of rural Croatia, markedly differing in the fat content of the diet. Two of the areas were closely similar in the total amount of fat, estimated at 85 to 100 g/day, but differed sharply in the kind of fats used.

In the "animal-fat" area (N=79), over 90 per cent of the fat intake was of animal origin. It was consumed in the form of lard, fat pork meat, smoked bacon and ham, and dairy products.

In the "olive-oil" area (N = 66) this vegetable oil, containing a substantially higher proportion of unsaturated fatty acid, covered a similarly high proportion of the total fat consumption. There was very little of dairy products and sea fish served as a principal of fresh meat.

In the third, "low-fat" area (N = 64) both animal and vegetable oil were used, in a total amount estimated to be below 50 per cent of that consumed in the other two regions.

Statistical analysis indicated that (1) significant linear age trends in serum cholesterol were present, (2) within the given age limits (19 to 59 years), there was no significant departure from linearity in the age trends of serum cholesterol for any area, (3) differences between linear slopes were not significant, but (4) the level of regression lines was significantly higher in the "animal-fat" than in the "low-fat" or the "olive-oil" areas. The corresponding age-adjusted values of serum cholesterol for age 40 years were 239, 211 and 201 mg/100 ml, respectively.

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Macromolecular Lipoproteins in Atherosclerosis: A Review

By LOUIS ROSENFELD, PH.D.*

ATHEROMATOSIS is a metabolic disturbance in which plasma lipids accumulate in the arterial wall. It is not an inevitable consequence of the wear and tear of aging but may be preventable and perhaps is also partially reversible.[1] It leads to atherosclerosis and to arterial occlusive disease which is responsible for more deaths and disability than any other disease in the United States.[2] At present there is no agreement on the etiology or treatment of atheromatosis. In the following review a summary is given of the more important physical and chemical features of recent investigations, with special attention to the role of serum lipoproteins as macromolecules. It is not intended as a general review of the entire field of metabolic aberration in atherosclerosis.

ANATOMY OF THE PROBLEM

Atherosclerosis has its inception as atheroma in childhood and usually becomes progressively severe with increasing age. The lesions of atherosclerosis develop under conditions generally regarded as normal, indicating an inherent susceptibility of the human species to this condition.[3] The deposit of lipid in the arterial wall has been variously ascribed[4] to (a) inhibition of lipid from the blood stream; (b) extravasation of serum, or of hemorrhage, from the arterial vasa vasorum; (c) reaction to injury of the intima; (d) necrotic debris of degenerated subintimal tissue; and (e) local production of lipid consequent to some disorganization of the intima such as mechanical strain, or to an abnormality of action of lipolytic enzymes. There is probably more than a single cause. The evolution of the lesion appears to be the result of a dynamic interaction of multiple factors. It seems that a predisposed person has anatomic or chemical characteristics that make him susceptible to deposition of lipids in the subintimal layers of the large and medium-sized arteries.[5]

A striking morphologic feature of these lesions is the great accumulation of cholesterol, its esters and other plasma lipids. The quantity so greatly exceeds that which can be regarded as originating from local destruction of tissue, that it is generally believed that the lipids infiltrate the intima from the blood plasma that bathes its surface.[3]

The intima is nourished directly by plasma within the lumen, and it is likely that this process is actively concerned in the causation of atherosclerosis. The intima of the blood vessels acts as a semipermeable molecular filter through which pass many of the constituents of the plasma.[6] Whereas the filtration pressure in all other tissues is the relatively low capillary or venous blood pressure, in the arteries the arterial blood pressure itself determines part of the movement of fluid across the intimal membrane into the subendothelial tissue spaces.[4] Possibly because of this high filtering pressure the arteries are vulnerable, and the sites of predilection to atherosclerosis are those that are subject to the greatest intravascular pressure. In hypertension the elevated hydrostatic pressure increases the volume of filtrate formed and the quantity of serum lipoprotein that diffuses across the vessel wall. This increases the possibility for incomplete removal and deposition of lipids in the meshes of the vessel wall.[7] But this cannot be the only explanation since experimentally the

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permeability of portions of excised veins to serum proteins and lipoproteins is much greater than that of arteries.[6]

The molecular size of substances in relation to the porosity of vascular walls is of first importance in determining their passage through or entrapment in the walls.[6] The smallest lipoprotein molecules pass through the vascular wall into the lymph, those of intermediate size are apparently caught intramurally, and the largest cannot enter the arterial wall at all. The so-called atherogenic lipoproteins fall into the intermediate group and only that portion of the cholesterol carried in the specific particles of intermediate size is deposited in the arterial walls.[1]

Although cholesterol is the basic constituent in the formation of ateromatous lesions of the arteries, hypercholesterolemia plays no more than a contributory role in their production. Deposition of cholesterol may be accelerated or exaggerated if its concentration in the plasma becomes excessive. To this extent hypercholesterolemia could act as a contributory cause of atheroma,[8] but measurement of total plasma cholesterol alone cannot serve as an index of atherosclerosis.[1,9] Cholesterol accumulates in the walls of the arteries when these are affected by degenerative processes or local injuries, but injury to the intima is not a necessary factor in the causation of the disease, though it may favor local manifestations and may determine the sites of predilection. Increased permeability is an important determinant in the genesis and localization of atherosclerosis. Permeability is increased by lack of oxygen, increase in acidity and by noxious substances such as histamine; whereas permeability is decreased by thyroid hormone, calcium, ascorbic acid and iodides. Deficiency of thyroid hormone greatly increases capillary permeability and this is reversed by administering thyroid extract.[4]

A new approach to the problem of atherosclerosis suggests that this condition is in reality the result of two defects;[10] one involves an error in cholesterol metabolism, while the other is manifested by a breakdown in the structure of the elastic elements in the media of arteries. The breakdown of elastic tissue may be observed to occur prior to the formation of atheromata.

PHYSIOCHEMICAL ALTERATIONS

Physical Variants: The ultracentrifugal studies of Gofman and his associates[9,11] have demonstrated the existence of an entire series of lipoproteins in human serum, differing from each other in such properties as hydrated density, molecular weight and chemical composition. Ultracentrifugal analysis of serum has shown that the serum lipids are carried in large complex molecules of different sizes and densities, called lipoproteins, which contain varying amounts of free and ester cholesterol, phospholipid, neutral fat and protein. They are classed according to their rate of flotation during ultracentrifugation in a medium of higher specific gravity, and are expressed in Svedberg units of flotation (S_f).

There are significant differences in these lipoprotein levels in fasting and nonfasting blood,[12] the molecules of smaller size being increased in the fasting state and those of larger size being increased in the nonfasting state. It would seem therefore that the lipoproteins of larger size are primarily involved in the early steps of the metabolism of exogenous food, probably largely of fatty foodstuffs. In the fasting person the increase in small lipoproteins suggests that this class is involved in a much later phase of metabolism of exogenous fatty food. Endogenous fat may probably utilize the same metabolic pathways.

The associations of increased concentrations of cholesterol in persons in the older age group with an increased incidence of coronary heart disease suggests that the high serum concentration of certain of these lipoprotein macromolecules may be of primary importance in the causation of coronary atherosclerosis. The concentration of these macromolecules can be reduced by dietary restrictions of fat and cholesterol.[13,14] The total concentration of cholesterol in the blood correlates with the frequency of atherosclerosis only when elevation of cholesterol is associated with elevation of this specific class of lipoproteins. It appears that the high concentration of these giant molecules, and not that of cholesterol, is significantly

associated with atherosclerosis and recurrence of myocardial infarction.[14] Although it has been claimed that the concentration of total serum cholesterol is significantly elevated in coronary heart disease over the level in the "noncoronary" population,[15] and that a tendency toward early and severe atherosclerosis accompanies persistent high levels of cholesterol, less than half the patients with myocardial infarction actually have hypercholesterolemia, and this is usually of a mild degree. In up to 25 per cent of patients with coronary disease there is no correlation between the concentration of total cholesterol in the blood and the distribution of cholesterol in these lipoprotein complexes.[1]

The particular classes of lipoprotein molecules of S_f 12–100, which have been related to the genesis of atherosclerosis, occur in very low concentration in children, young women and in species of animals in which atherosclerosis does not spontaneously occur. These molecules of low density, though present to a small extent in normal serum, also occur in much higher frequency and at a higher concentration in patients who have other diseases associated with excessive atherosclerosis;[11] but they are not always present in atherosclerosis.

Chemical Variants: In normal and atherosclerotic sera essentially all the cholesterol and phospholipid is combined with either the alpha- or beta-globulins as detected electrophoretically.[5,16] Normally, the ratio of cholestrol to phospholipid in the α- is much less than in the β-globulin. In persons who have survived myocardial infarction and in those with diseases known to predispose to atherosclerosis, there is a tendency for an increase of cholesterol and its ratio to phospholipid[17] and also of specific-sized molecules (Gofman). These patients have more cholesterol in the β fraction and less in the α than normal persons, indicating that the distribution of these fractions has a possible pathogenetic significance.[5] There is also a tendency to relative and absolute reduction of α-lipoprotein, and a relative and absolute increase in β-lipoprotein. Such changes may be apparent without hypercholesterolemia or significant elevation of the cholesterolphospholipid ratio of the plasma.

The widest deviations from normal are found in diseases known to predispose strongly to atherosclerosis such as diabetes, nephrosis and xanthomatosis.[5] In these diseases the distribution of cholesterol between the α- and the β-lipoproteins is more constantly disturbed than the other chemical variables. The per cent of the total cholesterol in the α fraction gradually decreases in various groups of persons in the following order: infants, young women, young men, older adults, patients who have survived myocardial infarction and patients with diseases predisposing to atherosclerosis. The lipid pattern of plasma from the umbilical cord of the newborn is strikingly like that of the rabbit and rat, two mammals that seldom, if ever, develop spontaneous atherosclerosis. The lipid pattern reveals low cholesterol, low cholesterol-phospholipid ratio, no specific-sized molecules, and a high percentage of total cholesterol in the α-lipoprotein. In survivors of infarction the distribution of cholesterol between the lipoproteins is more constantly disturbed than the other chemical factors but not consistently enough to be pathognomonic of atherosclerosis. The specific molecules of low density of Gofman may form a part of the β-lipoprotein increment. An abnormal distribution of cholesterol between α- and β-lipoprotein is much more likely to be significant in a young person than in a middle-aged or old person.

MACROMOLECULES AND CHYLOMICRONS

There is further evidence that lipoprotein of certain particle size is well correlated with atherosclerosis. When hypercholesterolemic rabbit serum or plasma is injected intravenously into a control rabbit, arterial lesions resembling atherosclerosis, may be seen within 48 hours. If this plasma is ultracentrifuged the upper fraction (containing the lipoproteins of largest size), when injected, produces no arterial lesions. Injection of the lower layer, however, is followed by appearance of typical lesions. Since both top and bottom fractions contain cholesterol and other lipids, specific molecular size becomes the important factor in atherosclerosis.[18] This too suggests that special macromolecules are responsible, and that

pathogenicity is much more closely related to the levels of certain cholesterol-protein complexes than to the level of the total plasma cholesterol itself. Foreign macromolecular substances (polysaccharide in nature) when injected into experimental animals, produce damage to the vascular walls in a manner closely resembling atherosclerosis.[19]

The particle size of the colloid lipoprotein molecules increases after a fatty meal. Patients, with conditions that are characterized by sustained hyperlipemia and that are known to predispose to the relatively rapid and severe development of atherosclerosis, show a hyper- and macrochylomicronemia similar to that following a fat-rich meal in normal persons. It has been suggested that the cumulative effect of many fatty meals over a lifetime, by producing recurrent showers of large lipid particles in plasma, may underlie the gradual development of human atherosclerosis.[20]

The degree of chylomicronemia is less and of shorter duration in younger people, and is dependent on the amount of fat ingested and not on the cholesterol level. In older people it does not return to fasting levels for as long as 24 hours, indicating an almost permanent increase of circulating fat particles. Ingestion of lipase or detergents with a fat meal reduces the hyperchylomicronemia in older people but does not greatly influence that of younger persons.[21] Secretion of pancreatic lipase and levels of blood lipase are significantly lower in older people, suggesting that the mechanism of fat digestion or absorption changes with aging.[22,23]

ROLE OF HEPARIN

The physiologically occurring anticoagulant, heparin, may play a role in the transport and metabolism of fat. Deficiency of heparin or a heparin-like substance may produce a blockage in utilization of the fat molecules. Heparin retards the development of atherosclerosis in rabbits receiving cholesterol. Clearing of alimentary lipemia *in vitro* is produced by plasma heparinized *in vivo*.[26] This indicates that heparin itself does not directly induce any alteration in lipoproteins but when administered intravenously, it may activate or stimulate the production of a substance in plasma having antichylomicronemic properties. Heparin appears to alter the physical state of the fat molecules, since the total lipid level is not altered. *In vivo* and *in vitro* action leads to an increase in α-lipoprotein concomitant with a fall in β-lipoprotein.[25] Following ingestion of fat, and after the administration of heparin,[24,25] it appears that larger lipoprotein molecules of very low density are normally broken down progressively in the direction of smaller lipoproteins of higher density. Low density β-lipoproteins and chylomicrons are rapidly removed from plasma through the action of a "clearing factor" whose activity is induced by administration of heparin. This "clearing factor" may be a lipolytic lipase which catalyzes the hydrolysis of the triglycerides of the chylomicrons but not of simple neutral fat emulsions.[25] Heparin is not surface-active but a decrease in surface tension accompanies the heparin-induced clearing of lipemic plasma, suggesting that a surface-active agent is formed when heparin is injected. This surface-active agent responsible for the clearing of lipemic plasma may be a heparin-phospholipid complex.[26]

It has been shown that the repeated injection of heparin decreases the severity of experimental cholesterol atherosclerosis.[24] In atherosclerotic patients, small doses of heparin may fail to clear alimentary lipemia as effectively as in normal persons.[27] Heparin clears the plasma by enabling fat to combine with protein. The lipoprotein thus formed passes easily through the vessel walls since it tends to be of smaller molecular size than the original lipid.

Since most individuals can utilize administered heparin in the manner described, a major physiologic error in diseases of lipid metabolism may be concerned with formation of heparin in mast cells or with the mechanism controlling its secretion.[25] The clinical use of heparin, however, is tempered by several disadvantages: it is expensive; it must be used intravenously; its action is brief; and it encourages hemorrhage, since it prevents the blood from clotting.

INFLUENCE OF SEX AND AGE

The marked difference in the two sexes in incidence and severity of atherosclerotic disease is not paralleled by any difference in cholesterol levels between men and women. Although atherosclerosis is not absent in all young women, its complications are seldom seen before the menopause.[5] In the twenties, thirties, and forties, men are much more frequently affected than women by coronary disease. In the fifties the predominant frequency in males diminishes relatively, and after 60 years the incidence among men is not much different from that in women. But there is considerable variation in severity from individual to individual at any age.

During the first two decades of life, no significant sex difference in level of S_f 12–100 is demonstrable.[12] There is a striking elevation in this level among men between 25 and 30 years of age and after 30; a general rise in the fifth and sixth decades, and then a decrease during the sixth and seventh decades. Women do not show this striking change from 25 to 30 years of age, but increases in concentration of S_f 12–100 occur slowly over the entire age span from 25 to 70 years. A level of S_f 12–100 essentially identical with that attained by men by age 30, is reached by women during the sixth decade. In the sixties and seventies the rising level in women exceeds that in men. Striking is the fact that the intima of the coronary arteries is considerably thicker in men, a difference present from birth.[28] It is of interest too that women have more mast cells. The latter are presumed to be a source of heparin which alters the physical state of the fat molecules.[24]

Constitutional, genetic, familial and hereditary factors may also operate in predisposing toward this disease.

Inasmuch as young women have a lower tendency to develop complications of atherosclerosis than young men and this difference in incidence is not apparent in women after the menopause compared to men of similar age, a study has been made of the effect of estrogen therapy in altering the lipid components and their distribution in abnormal serum. Administration of female sex hormones produces an increase of cholesterol in the α fraction and a decrease in the β fraction among survivors of myocardial infarction. In most cases there is also a fall in concentration of total serum cholesterol. Lipid levels following treatment approximate those of healthy young men.[5] When medication is stopped, the concentration and distribution of lipids return promptly to previous values. On the other hand, the male sex hormone promptly reverses the effects of estrogen, even when both are given together. This adverse effect disappears when testosterone is discontinued. The female hormones seem able to change the balance of the lipoproteins in blood toward a higher proportion of the smaller relatively stable molecules. This function may well be associated with the biologic need for efficient transport of large amounts of fat in women during pregnancy and lactation. But the feminizing action of the hormone goes hand in hand with its ability to prevent atherosclerosis. Since the concentration and distribution of the lipids are subject to hormonal influences, there may be a chemical reason for the apparent partial immunity of young women to complications of atherosclerosis.

LIPOTROPIC FACTORS AND EFFECTS OF DIET

The use of the so-called lipotropic agents, choline, inositol and methionine, is directed at mobilization and removal of the lipids from atherosclerotic lesions. The theoretic basis for this application lies first in their lipotropic action, and second in providing components of phospholipid, thus helping to keep cholesterol stabilized. Their use was suggested initially by the gross similarity of the fatty deposits in arteriosclerosis to those in fatty livers. Some fatty livers lose their fat after administration of these lipotropic agents. However, the analogy is superficial.[29] None of these lipid deposits are similar chemically or histologically to the lesions of arteriosclerosis. And not all types of fatty livers respond. In atherosclerosis and coronary arterial disease, a high ratio of cholesterol to phospholipid is the result of a proportionally greater increase in cholesterol usually accompanying these disorders. Lipo-

tropic agents tend to lessen this disproportionality by increasing serum phospholipids.

Colloid stability, observed to be decreased in serum of arteriosclerotic patients *in vitro* is increased by administration of lecithin and decreased by giving of cholesterol. One of the factors favoring the deposition of cholesterol in the intima is probably enhanced by the lack of sufficient colloid-stabilizing action owing to a decreased proportion of phospholipid in the serum. Phospholipids, by acting as emulsifying agents, have a stabilizing effect on the plasma lipids and serve to keep the lipoprotein complexes in relatively small size, resulting in a clear serum. With a low phospholipid concentration the particles are larger and the serum appears lipemic.[30] Some authors believe this ratio is of no more value as an index of atherosclerosis than is the total concentration of cholesterol itself.[31]

The better controlled studies of the action of inositol and choline in both rabbits and chickens have not demonstrated any effect of these agents either in preventing or curing arteriosclerosis, or in influencing the serum lipid pattern in a favorable manner.[29] Very few clinical studies of the effects of lipotropic agents on human arteriosclerosis have been reported, despite wide use of these compounds in medical practice. These agents may cause a fall in concentration of serum cholesterol in some patients, but on continued feeding, cholesterol returns to original levels. In clinical as well as in animal studies, it is always difficult to be certain that reductions in serum cholesterol levels following administration of lipotropic agents are not caused by secondary factors, such as loss of weight. This is likely to occur when choline or inositol are fed, owing to the production of anorexia and diarrhea by these compounds.[29]

There is no satisfactory evidence of the effect of lipotropic substances in prevention or treatment of human atherosclerosis, or of any specific influence on the serum level of cholesterol in man or experimental animal.[29]

There is support, however, for the value of low-fat, low-cholesterol diets.[32] Controlled human dietary experiments are difficult and costly. They must be prolonged because the significant time scale is long, and individual variability is large. But a significant effect of the level of dietary fat on serum cholesterol is evident in a few weeks in a person on a changed diet. However, differences of cholesterol levels are most pronounced when comparison is made between populations habitually subsisting on different diets. The average concentration of cholesterol in persons living on a high-fat diet (40 per cent of calories) is 25 to 50 per cent greater than the average in persons living on a low-fat diet (20 per cent or less). Statistical surveys of various segments of the population also indicate that there is a higher incidence of arteriosclerosis in those groups of persons whose diet is inherently richer in fats and cholesterol.[33]

Fat both of vegetable and animal origin must be restricted to obtain significant lowering of serum lipoprotein and cholesterol. Vegetable oil, which contains no cholesterol, will cause a rise in serum cholesterol levels in many persons whose lipoprotein has been depressed by restriction of total fat.[34,35] On the other hand, when unsaturated vegetable fats such as corn oil[36] or cottonseed oil[37] in the diet are replaced, respectively, by more saturated fats such as hydrogenated vegetable oil or lard, there is a resultant elevation over previous serum cholesterol levels in the animals tested. The fatty acids forming cholesterol esters in the liver were more unsaturated on a cottonseed oil diet[37] than when lard was the source of fat in the diet. Atheromatous aortas have a higher proportion of saturated fatty acids in the cholesterol esters than do normal aortas.[38] It would appear that the unsaturated vegetable oils in the diet are less atherogenic than vegetable or animal fats. This suggests the desirability of investigating the saturated and unsaturated fatty acid partition of the serum cholesterol esters.

Starvation in man and animals greatly reduces the concentration of serum cholesterol, especially the ester. In some nations subjected to near starvation or deprived of part of their usual lipid and/or caloric intake during war time, the incidence of myocardial infarction and generalized atherosclerosis fell to unusually low levels.[39] Whereas the more obese

tended to have a higher concentration of serum cholesterol and of S_f 12–100 molecules,[40] restriction of dietary fat resulted in the lowering of these lipoproteins.[13] Studies on autopsy material consistently reveal a much greater proportion of overweight persons have advanced atherosclerosis and coronary atherosclerosis.[41] Atherosclerosis is less severe and less common among chronic alcoholics who eat less, especially fat for which they often have an intolerance.

The possibilities offered by sitosterol and the soy bean sterols are promising. These plant sterols are absorbed into the body from the intestine to a much smaller extent than is cholesterol; and when they are fed together with cholesterol, they interfere in some unknown way with the absorption of excess amounts of dietary cholesterol, leading to prolonged decrease in circulating blood cholesterol.[42,43]

THE REAL PROBLEM

The tendency to assume that adult persons with no demonstrable signs of vascular disease are free from atheromatosis and thus differ qualitatively from patients with coronary occlusion or other definite evidence of atherosclerosis is generally invalid.[38] Comparisons of patients with atherosclerosis and "normal" persons of the same age and sex actually may represent comparisons between different degrees of severity and different anatomic locations of atheromatous lesions. Unless there has been a clinical sequel, atherosclerosis may be a silent lesion and may remain undetected even though it develops to an extreme degree.

The real problem is the prevalent, if not universal, chronic symptomless disease of early atheromatosis.[38] Coronary artery disease generally is a chronic progressive lesion rather than an acute process.[44] It is extremely difficult to recognize coronary atherosclerosis clinically in the absence of symptoms. No one test deviates in its results with sufficient constancy to permit its use in the clinical diagnosis either of the presence of atherosclerosis or of a tendency to its development.[5] Gofman and his associates[9,14,44] have accumulated much evidence showing a strong relationship between coronary artery disease and the concentration of certain serum lipoproteins. With these data they offer a method to evaluate an individual's degree of "accumulated coronary artery disease," and subsequently a means to predict for a particular individual of either sex and at any age, the quantitative outlook for the development of fatal coronary heart disease. In a recent report, however, tissue examination of aorta and coronary arteries of six autopsied persons in the 80 to 100 year group revealed a total lack of correlation between the degree of arteriosclerosis and atherogenic index before death.[45]

The results of a large co-operative study recently made by the National Advisory Heart Council reveal a difference of opinion between the group from the University of California (Gofman) and the investigators from the Cleveland Clinic (Page), Harvard (Stare) and University of Pittsburgh (Lauffer). The conclusions of the latter group are: while the elevation of serum lipoprotein and cholesterol was not of clinical use in the prediction of coronary heart disease, in individual cases such a finding may have useful applications in epidemiologic studies. The use of S_f 12–20, and S_f 20–100 lipoprotein measures, or related indices had "no advantage over the simpler measurement of cholesterol in the characterization of men prone to develop coronary heart disease."[46]

The problem is well stated:[46] "The difficulty of demonstrating an association of serum lipids with atherogenesis may be related to the inappropriate use of an American population, which is almost universally affected with atherosclerosis."

SUMMARY

Although aging and atherosclerosis are chronologically associated, the relationship is not one of cause and effect. Atheromatosis is a process conditioned by local and systemic metabolic factors. The cause of lipid deposition in arteries doubtless is related to changes in the concentration, composition and state of aggregation of the lipid substances in the blood. Physiochemical characterization of the serum lipoproteins in regard to particle size gives

better correlation with atherosclerotic heart disease than does the concentration of serum cholesterol. The distribution of cholesterol between the α- and β-lipoproteins may prove to have diagnostic value. Hypertension and vascular injury are contributory factors in production of atherosclerosis, since they alter the permeability of the arterial intima thereby facilitating deposition of lipid. Cholesterol in the diet is also a contributory factor, but ingestion of excess fat is apparently the primary factor concerned in the physical, chemical and physiologic processes that promote atherosclerosis.

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Dietary Studies in Ecuador

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WITH increasing world-wide interest in nutrition during recent years, various studies of food consumption, eating habits and nutritional status have been undertaken in countries around the world. As a part of its program in encouraging more adequate food production and consumption, the United Nations Food and Agriculture Organization (FAO) has participated in surveys of food consumption and eating habits, at the family level, in various of its member nations. This is a report of studies made in Ecuador, during 1953 and 1954, in co-operation with the Government of Ecuador represented by the Instituto Nacional de la Nutrición del Ecuador (INNE), and under the direction of the senior author.

ORGANIZATION OF THE PROJECT

The project had been under discussion between FAO and Ecuadorean government officials for several months prior to the arrival of the author who was to serve as the FAO nutritionist, under the technical assistance program, to plan and direct a series of dietary surveys. Two members of the INNE staff, one a graduate social worker (R.T.) who had been given a four-month fellowship in dietary surveys at the Instituto de Nutrición de Centro America y Panama (INCAP) in Guatemala City, and another a graduate nurse (R.O.) with training in dietetics and dietary surveys both in the United States and at INCAP, were assigned to work on the project. Later, upon the resignation of one of these workers, another graduate nurse (C.V.) and then a teacher (M.S.) joined in the work. These workers were responsible for the actual collection of data and were trained in selection of survey samples, determination of types of data to be collected, the mechanics of calculating, processing and interpreting data, and in some of the ways in which information thus gained might be made useful to teachers, health workers and others interested in teaching better nutrition. On each of the five surveys made, one or more local persons and/or agencies participated in some phase of the work. Food analyses were made available by the food analysis laboratory of INNE. Local personnel of the FAO Mission in Ecuador provided statistical and secretarial assistance.

DETERMINATION OF SURVEY AREAS

Ecuador is a country of approximately 100,000 square miles and a population of four million; it lies astride the equator, bounded on the west by the Pacific Ocean along a 600-mile coastline, on the north by Columbia and on the south and east by Peru. Ecuador is a country of contrasts; topographically it can be divided into three distinct areas, namely, the Litoral, the Sierra and the Oriente. Except for a narrow arid strip which follows the coast at some places, the litoral or the low area lying west of the mountains, is liberally supplied with rain and is covered with heavy vegetation. This makes up about one-fourth of the total land area of the country and has approximately 40 per cent of the population. East of this area, the Andes rise sharply, to heights of 18 to 20,000 feet. This region, the Sierra, is also about one-fourth of the total land area of the country and has approximately 58 per cent of the total population, the major part of the population living at altitudes above 8,000 feet. Beyond the Andes, to the east, lies the Oriente, which makes up approximately one-half of the total land area, with only 2 per cent of the population. It is

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mostly less than 1,000 feet in altitude, is covered with dense rain forest, and is inhabited largely by widely scattered indigenous tribes living along the rivers which are the headwaters of the Amazon. These three areas are more or less distinct socially as well as geographically.

At the time that the program of dietary surveys was intitiated, it seemed best to follow these natural divisions and to select, for study purposes, localities within each area which would be representative of the area. The first studies were made in the Sierra; one among a strictly indigenous rural population (descended from pre-Incan tribes) in the Otavalo Valley in the northern part of the country; one among the Mestizo* and White population in Cotocollao, a town of about 5,000, very close to Quito, the capitol city; and one among a Mestizo and White population of three parishes of low or median socio-economic level in the city of Cuenca, having a population of about 40,000, in the south of Ecuador. In the Litoral, the first area studied was the rural community of Quinindé, of White, Mestizo, and Negro population, about 75 miles up the river from the port of Esmeraldas. Here rainfall is heavy and vegetation is luxurious, the banana being the chief agricultural product. Later, a second study was made of the Mestizo population of fishermen living on the outer edge of the city of Manta, along the dry narrow strip which exists at that point of the coastline. Dangers of transportation along the swollen rivers of the Oriente during the rainy season, in order to reach the widely scattered tribes of that area, made it impossible to initiate any surveys along the headwaters of the Amazon at this time.

As Ecuador has been called the country of contrasts in respect to climatic, geographic and ethnic factors, so is it a country of contrasts in respect to activities of population groups. While the Otavalo weaver walks to town, carrying one or more lengths of woolen suiting to sell and returns carrying raw wool plus a few other purchases, this is a total of five or six miles and is usually only once a week; otherwise his is the sedentary life of the weaver. The so-called Panama hat weaver of Cuenca is an arduous worker at a tedious task, but the physical activity involved is not great. The Cuenca housewife will walk to the market daily, but even in the city, housekeeping tasks call for little physical effort. Houses are small; furniture and furnishings are very limited in quantity and require little or no care; both food preparation and care of clothing are kept very simple. While the average Ecuadorean works hard for a living he does not necessarily put forth a great amount of physical activity. Even the fishermen and stevedores included in these studies worked relatively few hours of the week at these more strenuous tasks. The artisan, shopkeeper or small businessman, in most parts of Ecuador, may work very long hours but under sedentary conditions, often in his own home. In these studies, we had none of those people who, in some parts of Ecuador, may carry heavy burdens for long distances. Some other comments concerning physical activity in the various areas studied will be found in the descriptions of those areas.

* The word Mestizo, wherever used in this paper, indicates a racial group of mixed indigenous and White (usually Spanish) stocks.

COLLECTION AND TREATMENT OF DATA

As mentioned earlier, data were collected by local persons, trained for this project, and working under the direction of the senior author.

For all surveys, the "family" was taken as the unit for study. Data collected included quantitative food consumption data for a period of seven consecutive days as well as qualitative data on food habits, food preparation, mode of living, etc. In order that quantitative data could be properly processed, other data including age and weight of each family member, obvious physical condition such as illness, pregnancy or lactation, and factors concerning activity were noted. Prices of purchased foods, land ownership, harvest seasons and other socio-economic data have also been obtained. Survey samples were selected by random sampling methods except in the case of Otavalo.

For actual collection of data after one or two preliminary visits, each family was visited twice daily, for seven days, (five days in

TABLE I

Average Consumption of Calories and Nutrients per Capita per Day and Average Percentage of Adequacy in Respect to Each

Item	Sierra						Litoral			
	Otavalo (18 families)		Cotocollao (30 families)		Cuenca (50 families)		Quinindé (25 families)		Manta (16 families)	
	Consumption	% of adequacy	Consumption	% of adequacy	Consumption	% of adequacy	Consumption	% of adequacy	Consumption	% of adequacy
Calories	1,697	86	1,705	84	1,843	92	2,035	100	1,543	77
Protein—total g	55	100	51	91	53	93	56	97	54	95
Protein—animal, g	2	*	19	*	20	*	29	*	35	*
Fat—total g	22	*	33	*	43	*	42	*	21	*
Fat—animal, g	8	*	22	*	28	*	31	*	14	*
Calcium—g	0.3	33	0.5	50	0.6	60	0.4	40	0.2	22
Iron—mg	20	200	17	170	17	170	13	130	8	80
Vitamin A—I.U.	3,548	94	3,732	98	4,257	110	8,729	218	8,183	211
Thiamine—mg	2.0	200	1.1	110	1.0	100	0.9	92	0.5	50
Riboflavin—mg	0.9	69	1.2	86	1.5	107	0.9	64	0.7	47
Niacin—mg	16.4	166	22.9	229	13.4	134	13.4	131	10.2	102
Vitamin C—mg	155	254	105	172	79	127	115	169	103	158

* No available recommendations.

Otavalo). All foods were weighed in grams in the raw state, only the edible portion being weighed in so far as was possible. Corrections were made for waste, visitors, absentees and food fed to animals. Quantitative dietary data have been calculated for calories and nutrients by use of provisional food composition tables[1] prepared in Ecuador by the food analyses section of INNE. Where various analyses were still lacking, supplementary tables[2,3,4] were used.

Recommended allowances for comparative purposes were from a table[5] based on recommendations of the National Research Council U.S.A.,[6] and FAO.[7] Recommended levels for calories, thiamine and niacin were adjusted for temperature, weight, age and sex for adults. For adolescents these levels were calculated for the weight of the average male or female adult in the community. Recommendations for children are the same as given by the National Research Council and recommended by FAO for use in all population groups. Calories were calculated for moderate activity.

RESULTS AND DISCUSSION

The quantitative data on food consumption for each survey have been calculated and interpreted in such a manner that comparisons can be drawn between population groups with respect to nutrient intake in grams, relative adequacy of nutrients, and consumption of actual foods of the more important food groups. Such comparisons need not be limited to population groups within Ecuador, as methods employed for interpreting and presenting data are those in general usage. These data are presented in Tables I and II. Table III indicates percentage distribution of protein among the various food sources. Table IV shows the percentage contribution of proteins, fats, and carbohydrates to total calories.

Also, the actual state in which foods were used, when consumed by 10 per cent or more of families, has been recorded. Due to limited space, these data are not included here, and are probably of particular interest only to persons working in Ecuador or in other countries having a similar food supply.* Maize was chosen as the more interesting of the cereal foods because of the possible nutritional implications, the variety of ways in which it is used, and the great contrasts between the various population groups studied, with respect to its use.

* Published in Spanish by the Instituto Nacional de la Nutricion del Ecuador; also in English obtainable upon request from the senior author.

TABLE II

Average Consumption of Various Foods per Capita per Day for Entire Survey Group and Percentage of Families Consuming Each

Cereals and products[a]	Sierra						Litoral			
	Otavalo (18 families)		Cotocollao (30 families)		Cuenca (50 families)		Quinindé (25 families)		Manta (16 families)	
	% families consuming	g/ capita/ day	% families consuming	g/ capita/ day	% families consuming	g/ capita/ day	% families consuming	g/ capita/ day	% families consuming	g/ capita/ day
Maize[b]	100	146	100	65	98	76	36	3	37	3
Wheat	40	8	90	36	94	54	100	40	100	15
Rice	6	*	97	39	100	55	100	98	100	98
Barley	83	38	87	31	50	9	32	3	6	*
Quinoa	61	15	7	1	—	—	—	—	—	—
Rye	—	—	3	1	38	23	—	—	—	—
Oats	—	—	70	7	44	3	100	15	75	7
Starchy roots,[c] tubers, etc.	61	59	97	281	100	152	100	94	94	21
Pulses, nuts, oil seed[d]	100	116	87	14	88	30	92	27	94	8
Vegetables	100	294	100	63	100	66	92	43	100	15
Fruits (except bananas and plantain)	—	—	80	17	64	13	84	45	100	19
Bananas and plantain[e]	—	—	83	57	72	33	100	256	100	329
Meat, chicken	56	8	90	53	92	55	100	102	88	19
Fish	—	—	—	—	8	1	40	7	100	150
Eggs	11	*	33	2	64	4	68	9	25	1
Milk, cheese[f]	17	13	93	266	100	332	96	268	100	80
Fats, oils	100	7	100	11	100	15	100	19	100	11
Sugars	72	18	100	76	100	82	100	82	100	57
Chocolate, cocoa	11	*	67	2	38	2	72	3	50	1

* Indicates less than 1 g.

[a] Bread weights reduced by 1/4 to be comparable with air-dry grain.

[b] Weights of hominy and fresh mature maize reduced by 2/3 to be comparable with air-dry grain. Weights of fresh tender maize reduced by 3/4 to be comparable with air-dry grain.

[c] Weight of dried oca multiplied by factor 2 to be comparable with fresh oca. Weight of yuca flour multiplied by factor 3 to be comparable with fresh yuca.

[d] Weights of fresh or cooked legumes of all classes divided by factor 2 to be comparable with dried legumes.

[e] Weight of banana flour multiplied by factor 4 to be comparable with fresh bananas.

[f] Weight of cheese multiplied by factor 7 to be comparable with liquid milk. Weight of dried whole milk multiplied by factor 7 to be comparable with liquid milk.

Since food consumption and food habits cannot be adequately studied without reference to cultural, social and climatic factors, a brief description of each area studied is included. With these are some comments pertinent to nutrient consumption and possible adequacy or inadequacy. These are purposely kept to a minimum, for it must be borne in mind that this was solely a study of food consumption and eating habits, not of nutritional status.

Table I indicates a low average consumption of calcium in every area studied. In Manta, where it was lowest, 75 per cent of the families consumed an amount less than 25 per cent of the calculated recommendation, while no single family consumed as much as 50 per cent of that recommendation. In no area studied was there any single food other than milk (or cheese) which furnished substantial amounts of calcium. In view of recent findings reported by Hegsted,[8] it would be inappropriate to assume that serious calcium shortages do exist among any of these groups without confirmatory clinical and laboratory studies.

In every area studied, vitamin A (as caro-

tene) is available, though the pre-formed vitamin is generally in very low supply. In Manta every family met the full recommendation due, to a considerable extent, to the large amount available from bananas, a staple food. In Otavalo, and to a lesser extent in other areas of the Sierra, vitamin A is available from a limited number of good food sources. Some families received very large quantities and others almost none during the survey period, even though the average intake for the group may have been close to the recommendations.

Only in the Otavalo group, despite the extremely low intake of meat and other animal products, did every family meet the recommendations for iron, thiamine and niacin. In no other group did all families meet the calculated recommendations for any one of these three nutrients. Higher intakes of whole grain cereals and legumes in Otavalo accounted for much of this difference.

Vitamin C is reasonably well distributed among available food items; those foods which were the most important sources in the various areas, during the survey periods, were plantain in Quinindé and Manta, zambo (a squash) in Otavalo, potatoes and turnip greens in Cotocallao and these with a variety of other roots in Cuenca. However, none of these are eaten raw and some may be stored for relatively long periods at certain times of the year. In the Institute of Nutrition, there are as yet no available data for vitamin loss during storage and preparation of foods.

Cereal grains, roots and tubers are important components of the basic diet in the areas studied in the Sierra. In Otavalo the legume is also a basic food, high in carbohydrate. In the coastal areas, these foods are, at least in part, supplanted by the banana, often considered to be poor as a basic carbohydrate food because of its low quality protein. However, those population groups studied, who used the banana in amounts up to 330 g/capita/day, are probably not appreciably low in good quality protein intake. A group of plantation workers, living on the plantations and out of easy contact with the shopping center at Quinindé, would probably present an entirely different dietary picture.

The consumption of animal products is relatively low in the Sierra, especially among the rural groups. The indigenous people in the Otavalo area do not and apparently never have hunted or fished. Generally, animal products are consumed at home only by those families beginning to break away from tribal customs. The average consumption of total protein was relatively constant in all areas studied varying between 51 to 56 g/person/day.

TABLE III

Percentage Distribution of Protein Among Several Food Sources

Item	Sierra			Litoral	
	Otavalo	Cotocollao	Cuenca	Quinindé	Manta
Products of animal origin	3	37	38	51	fish: 55 other: 10
Pulses, nuts, oil seeds	43	6	11	11	4
Maize and maize products	35	10	9	—	—
Rice	—	—	—	15	16
Other cereals	11	26	32	12	7
Bananas and plantain	—	—	—	4	7
Other foods	8	21	10	7	1

TABLE IV

Contribution of Proteins, Fats and Carbohydrates to Total Calories (percentage)

Item	Sierra			Litoral	
	Otavalo	Cotocollao	Cuenca	Quinindé	Manta
Proteins	13	12	11	11	14
Fats	11	17	20	18	12
Carbohydrates	76	71	69	71	74

The proportion of animal protein, however, varied from 3 per cent in Otavalo to 65 per cent among the fishermen.

A few foods, unknown in many areas of the world, are of particular interest because of rather exceptional nutritive values and deserve brief mention here.

Quinoa (Chenopodium quinoa) is a cereal which grows higher on the mountains than other cereals and is used by the rural indigenous

people over a large part of the Sierra. Among cereals grown in Ecuador, it ranks with the best in all the more important nutrients and is appreciably higher than others in calcium. The calcium values for Quinoa, wheat, oats, rye, barley, rice and corn, in mg/100 g, are 72, 52, 52, 51, 38, 14 and 8 respectively.[9]

The naranjilla (Solanum quitoensis, Lam) which grows only in Ecuador is an important source of vitamin C.[9] It is inexpensive and well liked as juice or for flavoring puddings or cereal gruels.

Chocho (Lupinus sp.) is a legume grown and used by indigenous people in some parts of the Sierra. It is an important source of vegetable protein, having more than twice the protein in the commonly used peas and beans and 50 per cent more than peanuts and soya beans.[9] As is customary in Ecuador in the case of other legumes, it, too, can be made into flour and used as a thickening agent in food preparation.

OTAVALO

The Otavalo data were obtained from two indigenous villages, namely Peguche and La Bolsa, with populations of approximately 800 and 225 respectively.[10] These villages lie close to the city of Otavalo, at the head of a valley running between the two cordilleras of the Andes. The altitude is 7,396 feet. The mean annual temperature is 57.4° F and mean annual rainfall 42.9 in.[11]

Peguche residents are land-owners. La Bolsa is part of a large hacienda. In both villages, each family grows corn, beans, other cereals, potatoes, and other starch roots and zambo (a squash) in a small plot surrounding the house; in La Bolsa, however, half the crop goes to the hacienda owner. Leafy vegetables used are not cultivated.

Both Peguche and La Bolsa are communities of weavers. In Peguche the Spanish loom is used and woolen suiting is the chief product; in La Bolsa the indigenous loom is used for weaving ponchos (the overcoat of the Andean male); two types of spinning wheels are used in both communities.

Most foods are produced at home. Principal food items purchased for use at home are beef fat, unrefined salt and unrefined sugar. These, especially fat and salt, are expensive and are used in small amounts. A piece of fat the size of one's thumb or smaller may season a dinner for six. Sugar is often used for flavor in those same dishes which at other times are seasoned with salt, as humitas (a traditional food made of mature green corn, ground and wrapped in husks for steaming), cereals and squash. Since the use of animal food is so limited, it seems that the total salt intake must be very low. While no quantitative measure of salt used was possible, the senior author estimates the daily intake of sodium per person to have been under 2 g and perhaps no more than 1 g.

It was impossible to obtain quantitative data on foods eaten at the Saturday fair in Otavalo, though it was observed that these foods do differ from those used at home in some important respects. Foods sold in the market, and obviously eaten by some members of the study families, include fried meat chips, a stew of viscera, a variety of breads, bananas, oranges and other fruits. Since these, especially the meat product, are sold in very small amounts, and only to the older members of the family who go to the fair, it is improbable that these affect the complete diet to a very great extent.

Quantitative data for a five-day period indicate a diet which is, perhaps, better than is generally assumed for this population group. Further information, concerning utilization of plant proteins in general and the amino acid content of specific legumes in use in the area, is necessary for drawing definite conclusions relative to protein adequacy. Of special interest here are findings reported in a recent paper by Hegsted, *et al.*,[12] and earlier work reported by Hegsted, *et al.*[13] and Bricker, *et al.*[14] Further information concerning niacin will have special interest value because of its relationship to tryptophan, especially where corn is a basic food and where consumption of animal protein is low. Low calcium intakes and newer research relative to calcium utilization and needs[8] in Peru indicate a need for clinical work before any definite conclusions can be drawn in respect to this nutrient. Calories may be somewhat low; however, at the time of this study when no planting was being done, life in

the villages was more or less sedentary. The low intake of fat, especially of animal fat, is of interest, as well as the low-salt intake already noted. Vitamin C intake would no doubt be lower at another season when stored foods are used. At this time, there are no values available in Ecuador for loss of this and other nutrients in food preparation.

COTOCOLLAO

Cotocollao is a more or less typical Spanish town of 6,550 population,[15] lying about five miles north of Quito, the capitol city, and connected with Quito by a good paved road. It is at an altitude of 9,184 feet. The mean annual temperature is 55.9° F and the mean annual rainfall 31.3 in.[11]

The population is largely Mestizo, though a few indigenous families are found, and the predominance of indigenous stock is quite obvious in many. Perhaps the chief industry is pottery-making, though many small merchants, bakers, tailors and shoemakers care for the needs of the community. In the survey sample, no person commuted to Quito to work. Many families have gardens, and considerable quantities of onions are grown in and about Cotocollao for the Quito market, thus becoming a money crop of some importance.

Data show definite tendencies away from the diet followed by the indigenous group through the use of more meat and milk and less legumes; more refined cereals; more bread and pastes made from wheat and less corn; more rice and potatoes in place of other roots and tubers. The diet is better than the Otavalo diet in respect to calcium and riboflavin. Calories as calculated are somewhat low by comparison with the standards used. However, many of the adults do have sedentary occupations.

Fat consumption is higher than in Otavalo and the percentage of animal fat is much greater; the diet would nevertheless be considered low in fat by North American standards. Total protein is somewhat less adequate than in Otavalo but the animal protein is much increased. Very high niacin intake is in part to be attributed to the large per capita consumption (261 g) of a potato of very high niacin content.

As in most Mestizo populations in Ecuador, coffee is well liked, usually with sugar and a large quantity of milk. It is definitely preferred with milk, especially for breakfast, and is usually taken black only if the family cannot afford milk. A strong black coffee called "tinto" is also used, especially after other meals, but not regularly by the poorer families. It was observed that nearly all families in the Cotocollao study, where milk was readily available, did have it at least for the morning coffee, even though a fair percentage of the families would be considered quite poor. It is of interest to nutritionists that when milk is so used, it is shared by practically every member of the family.

With a higher consumption of animal products and a more refined salt more readily available, the sodium content of the diet is undoubtedly greater than in Otavalo. Salt is still relatively expensive however, and it was observed to be used in limited amounts. It is estimated that sodium consumption would probably not exceed 3 to 4 g/person/day or approximately one-half that in the United States.

CUENCA

Cuenca, one of the principal cities of Ecuador, has a population of 39,938.[15] It is situated in the southern part of Ecuador, at an altitude of 8,331 feet.[16] The mean annual temperature is 56.7° F and the mean annual rainfall 29.8 in.[11]

The survey sample was selected from three barrios or parishes, known to be areas of median or low socio-economic level. The population of the city is Spanish and Mestizo, though many indigenous groups live both north and south of the city and set up large daily markets of food products and other items within the city. The chief agricultural product of the area is sugar cane; the chief manufactured article the Panama hat. The larger part of the population of the city itself is Mestizo; every family of the survey sample was so classified. Cuenca is proud of its Spanish heritage and its cultural advantages; it is a city of many beautiful churches, a university and a teachers' college,

and good private and municipal schools at both primary and secondary levels.

There is a greater usage of refined cereals here than in Cotocollao, and quinoa, a cereal grown high in the mountains and well-liked by the indigenous people, did not appear at all among the families of the survey sample for the seven-day period. Corn is a basic food, usually used as mote or hominy which is made from dry corn without the addition of ash or any alkaline salt. It may be eaten as often as three times daily.

Due to the relatively high consumption of milk and cheese, intakes of calcium and riboflavin are greater than in any other survey sample. Apparently, in none of these areas was any other food eaten which would furnish amounts of calcium or riboflavin that would alter the relative importance of milk and cheese as sources of these nutrients.

As in other areas, actual caloric needs may well be less than calculated due to the sedentary work of many men and very light housekeeping chores.

Fat consumption, though highest of all groups studied, furnishes only 20 per cent of total caloric intake. The ratio of animal fat to total fat does not differ from that for Cotocollao. Values for total protein as well as the ratio of animal protein to total protein are the same for Cotocollao and Cuenca.

Again, as in Cotocollao, it is estimated that the daily sodium consumption would probably not exceed 3 to 4 g or approximately one-half that in the United States.

QUININDÉ

Quinindé is a rural village in the low tropical area of Ecuador which lies along the length of the coast, extending east to the first cordillera of the Andes. The village is situated at the confluence of two rivers, some 75 miles up the river from Esmeraldas, the seaport from which bananas from the area reach the world market. Though there has been a village at this point for many years, it consisted of some half-dozen houses until the road was opened to Quito (130 miles) in the late 1940's. At the time of the study there were more than 100 houses and some 800 to 1,000 inhabitants in Quinindé proper.[10] This population was made up of both Mestizos from the Sierras and Negroes from the coast, the latter predominating in number. A considerable number of foreigners are to be found in or near Quinindé, both as plantation owners and as employees of a foreign-owned banana company. The village is the trading center for quite a large area. Practically all land in the area which is readily accessible by river or road is under cultivation in bananas.

Quinindé is at an altitude of 262 feet.[10] The mean annual temperature is 77° F.[11] Though there are no available figures for mean annual rainfall, there are quite heavy rains for six months or more beginning in January.

This was the first group studied for which the caloric intake equaled the calculated recommendations for calories. As in all cases, calories for adults were calculated for moderate activity. It is felt that this may actually come closer to actual needs than in other areas. A number of men in this group were stevedores or worked in the plantations, doing reasonably heavy work. It was noted, however, that many of these did not regularly work as much as a five-day week, depending to a certain extent upon weather and sometimes, apparently, on choice. Household tasks are light and many women as well as some men would have been considered as sedentary had actual activity of individuals been evaluated. Most of the Negro men, who do the heaviest work, show good musculature but decided leanness, while among children, there seem to be many who are tall but quite thin and with poorly developed muscles. Some women among the Negro population should be classified as somewhat obese.

Of all nutrients in Quinidi, calcium and riboflavin are in shortest supply (Table I). It is interesting to note that average protein consumption is not poor and despite high prices more than half is of animal origin. Most of the milk used was in the form of an imported dried whole milk. The variety of meats and fish used was larger than in other areas studied.

Increased consumption of animal products increased sodium intake in this area; however, at the same time, bananas and plantain, which are very low in sodium and which were never

observed to be seasoned with salt, did replace some of the cereals and tubers used in the Sierra. Again it is estimated that sodium consumption would probably not exceed 3 to 4 g/person/day or approximately one-half that in the United States.

MANTA

The Manta group was composed of fishermen living on the edge of Tarqui, a section of about 500 families on the eastern side of Manta, a growing commercial city of approximately 20,000 population.[15] Fishing is an important industry; fish brought in are shipped to the Sierra, by air, either as fresh or quick-frozen, exported as quick-frozen, or used for local consumption. For only a few months at the time of this study, a canned tuna was being produced for the first time.

Manta is at sea level. The mean annual temperature is 77° F and the annual rainfall varies from a trace to 15.6 in.[11]

Neither Tarqui nor Manta has a municipal water supply. Water is brought in large trucks and sold to long lines of people who await each truck's arrival. Drinking water, sold from kegs transported by burros, is available to families of considerable economic means.

The population of Manta is largely Mestizo, with a few Negroes, Chinese, East Indians and Whites; the Whites from a number of European countries or the United States. The fishermen are Mestizo. While indigenous groups, with indigenous habits, are not found, the fishermen are probably descended from tribes who fished in these waters many generations ago. These coastal tribes have recently been identified with the Mayans. The Incans are not known to have ever been in this area.

Table I indicates a very low caloric intake for Manta subjects. It is felt that this figure is without doubt too low. Some error has probably been introduced by using too low a fat value for fish. Since few types of fish had been analyzed in Ecuador at the time of this study, a value for salt-water fish from the Institute of Nutrition in Columbia has been used. The same value is being used for all fish, though four different types were commonly used by families of the survey sample during the study period. The value used was moderately low in fat. In cases where the daily per capita consumption averages 150 g, and the value is markedly low in relation to the true fat content of the fish consumed, there would be considerable difference between the actual average consumption of calories and that calculated in this study.

No other group in the entire survey appeared to be as physically fit as did the young men of Manta. They are relatively short, seem to have excellent musculature (the upper part of the body being most developed) and have no appearance of leanness or obesity. Some women are obviously overweight. The caloric recommendation, as in all studies, was calculated for moderate activity. Although the fisherman expends considerable energy while bringing in the catch, this is not for a prolonged period and much of his day may be spent at sedentary tasks such as making and mending nets. Again, household tasks are light.

No other group studied presented such a low calcium intake. It was impossible to get information indicating that any fish bones were actually consumed. Also thiamine and riboflavin intake are lower than in any other group.

The high proportion of protein which is supplied by animal sources, especially fish, is shown in Table III. It is also of interest that where three meals a day are routine, there were very few meals at which no flesh food was served.

The consumption of flesh foods is relatively high here, but intake of milk and cheese is lower than in any other area studied with the exception of Otavalo. Total sodium intake per person per day, from natural food sources, is probably not greatly different than in Quinindé and again as in Quinindé, bananas and plantain replace much of the cereals and tubers used in the Sierra. It is estimated that in Manta, also, total sodium intake per person per day would probably not exceed 3 to 4 g.

SUMMARY AND CONCLUSIONS

Quantitative data on family food consumption in five areas of Ecuador are presented together with some description of the climatic, racial and socio-economic factors characterizing each area.

While no definite conclusions as to actual adequacy of the various diets can be drawn without clinical studies, data do include adequacy in percentages of generally used and well-defined standards.

Though it is well understood that food supply is not over abundant in any area studied, it can be pointed out that in every area most nutritents (with the notable exceptions of calcium and animal protein) are available in reasonable supply, and a more nearly adequate intake could be assured to more people through education at the family level. Foods which are important to the nutrient content of the present diet and which are well-accepted, though perhaps not popular with all population groups, must not be overlooked in agricultural and economic planning.

Data indicate that calories are, perhaps, in somewhat short supply. The intake of some other nutrients is also low in a relatively large percentage of families, and some families do far less well with respect to other nutrients than with calories. Unless caution is exercised in increasing caloric consumption, there is a possibility that other deficiencies may develop through imbalances. Increased production of food fats, which is taking place through a growing vegetable oil industry in Ecuador, can be most important in helping to alleviate caloric shortages. However, increased availability of food fats which are generally low in nutrients other than calories may necessitate more emphasis on nutrition education rather than less.

Also, as elsewhere and in other times, the rural inhabitant moving to an urban area where he will no longer produce his own food supply but will be dependent upon cash with which to purchase it, will likely find the greatest difficulty in providing an adequate diet. While economic and industrial growth will bring more people to urban areas, improved agricultural methods and transportation, which are being given much attention in Ecuador at this time, will make a better food supply available to more people. As more people can enjoy greater opportunities in food selection, a better understanding of food needs and food values gains added importance.

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Comparative Protein Repletion in Cancer and Non-Cancer Cachexia

WITH SPECIAL REFERENCE TO CHANGES IN BLOOD VOLUME AND TOTAL CIRCULATING PLASMA PROTEIN AND HEMOGLOBIN

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THE present report is a continuation of a previous study[1,2] dealing with the pattern of nutritional recovery in cancer and non-cancer cachexia. Particular attention is given herein to changes in plasma volume, red cell volume, and total circulating plasma protein and hemoglobin, which were not measured in the previous study. Weight gain and nitrogen balance were determined simultaneously.

PREVIOUS WORK

The clinical symptoms and signs of starvation have been graphically described in many clinical and experimental studies,[3-10] and will not be reviewed here, nor will the extensive investigation in animals be discussed. It has been noted that in human starvation, plasma protein and hemoglobin concentrations usually fall, although essentially normal values are often found. In chronic infection or cancer, the expected falls in plasma protein and hemoglobin concentrations have been more pronounced and consistent. Changes in the circulating blood volume and total circulating plasma protein and hemoglobin have also been recorded,[8,11-13] but only as single observations. Few repeated measurements of absolute changes during clinical starvation have been made. However, an expansion of the extracellular fluid space as shown by the appearance of peripheral edema is well known and has been frequently observed in malnutrition.

During repletion, changes in circulating volumes and total circulating proteins, have been reported occasionally for short periods but rarely for periods as long as a month or more. Long term observations have been made by Holmes[14] in non-cancer patients, and by Homburger[15] and Waterhouse[16] in patients with cancer. In these reports, observed weight gain was frequently less than that expected on the basis of nitrogen retention. Two patients with gastric cancer observed by Homburger for 26 and 108 days during positive nitrogen balance showed little change in total circulating plasma proteins and a variable change in plasma volume. The most complete and controlled long term experimental study of starvation and repletion in human volunteers by Keys, *et al.*[5] will be commented on later. It should be mentioned, however, that the depletion diet employed in the last mentioned study was primarily low in calories since it contained about 50 g of protein per day.

METHODS

Eight malnourished patients were studied, four with and four without cancer. In the four non-cancer patients, body weight losses were 19 to 38 per cent. The diagnoses were brain concussion, fracture of the mandible,

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senile psychosis and healed pyelonephritis. Nitrogen balance was measured from 27 to 106 days with average daily intakes of 2,630 to 4,110 cal and 163 to 247 g of protein. Thereafter nitrogen balance studies were discontinued, but observations of circulating volumes and proteins were continued to a total period of 47 to 126 days.

In the four patients with locally persistent and metastatic cancer, body weight losses were 13 to 45 per cent. The diagnoses were: carcinoma of the cervix, post-radiation; palliative resection of carcinoma of the rectum; carcinoma of the breast, postoperative persistence; and carcinoma of the esophagus, nonresectable. Nitrogen balance in these patients was measured for 19 to 44 days on average intakes of 1,820 to 3,160 cal per day, including 120 to 190 g of protein. These patients were exceptionally far-advanced and all succumbed within three days to six weeks after our studies were discontinued. Unlike the cases reported previously[2] this circumstance prevented higher intakes for longer periods.

TABLE I

Primary Measurements in Non-Cancer Patients During Repletion*

Patient age, % wt. loss	Time (days)	Body wt. kg	Alb.	Glob.	Hb	PV	RCV	Accumulated N balance g
1. B. R. (male)	0	44.5	4.3	3.4	12.2	2,560	1,725	0
19	15	47.2	4.0	2.4	12.2	2,620	1,510	
19%	27	48.6	4.0	2.8	11.2	2,650	1,890	
	28	49.5	4.1	3.0	12.8	2,510	1,760	478 discon-
	41	52.3	4.1	2.9	12.3	2,730	2,045	tinued
	93	55.0	3.7	2.7	13.0	3,260	2,350	
	100	55.0	4.1	2.5	13.5	3,180	2,330	
	116	57.2	4.3	2.5	14.2	2,945	2,185	
2. C. H. (male)	0	40.9	3.2	3.2	10.9	2,950	1,700	0
54	15	42.7	3.4	3.6	12.0	2,340	1,711	
33%	30	45.4	4.0	2.7	14.5	2,710	2,330	486 discon-
	47	45.5	3.8	3.0	14.7	2,635	2,330	tinued
3. J. R. (male)	0	44.1	3.5	2.5	13.3	2,730	1,880	
73	28	47.7	3.4	2.3	12.6	3,810	1,970	288 discon-
19%	42	50.0	3.3	2.1	13.2	3,795	2,035	tinued
	72	47.7	3.8	2.1	13.0	3,605	2,070	
4. V. J. (male)	0	45.0	2.5	2.4	11.4	2,525	1,010	0
64	14	47.2	3.4	2.9	10.9	2,825	1,275	
38%	23	50.9	3.6	2.6	12.2	2,400	1,620	
	32	50.9	3.1	2.2	13.2	2,850	1,670	446
	41	52.7	2.9	3.8	11.2	3,170	1,780	
	57	54.1	3.7	2.7	12.2	3,070	1,870	
	79	59.0	3.9	2.6	13.0	2,810	1,750	
	91	62.2	3.4	3.4	13.0	2,800	1,925	
	106	65.0	3.4	3.2	13.9	2,920	2,130	1,607 dis-
	126	66.8	3.9	1.8	13.9	2,680	2,055	continued

* Key to Tables I and II:
Alb. —plasma albumin (g/100 ml)
Glob.—plasma globulin (g/100 ml)
Hb —hemoglobin (g/100 ml)
PV —plasma volume (ml)
RCV—red cell volume (ml)
N —nitrogen (g).

The sole food intake consisted of a feeding mixture of known and uniform composition and suitable for tube feeding if required.[1] Urinary nitrogen losses were measured by a macro-Kjeldahl procedure,[17] 10 per cent of the nitrogen intake being added as an estimate of losses in the feces, skin, hair, and nails, an approximation based on daily fecal nitrogen measurements made over periods of a week or more in several cases. Inlying urethral catheters were used in all female patients.

The plasma volume was measured at weekly intervals with Evans blue dye (T-1824) according to a modification of the method of Gibson and Evelyn.[18] The concentrations of total and fractional plasma proteins, non-protein nitrogen, hemoglobin and the hematocrit were measured at the same time.[17,19–21] (The values of plasma non-protein nitrogen were measured but not reported as there was no change from the normal in any patient.) A single standardized pipette was used for all hemoglobin determinations. The red cell volume and the total circulating plasma protein and hemoglobin were calculated from these values. No correction was made for differences in venous and total body hematocrits. Nitrogen balance studies were not begun until all the patients had become accustomed to the hyperalimentation regimen for several days and the urinary nitrogen losses stabilized on the high nitrogen intakes. The patients were weighed daily.

FINDINGS

Individual case reports are presented first, followed by a summary of certain changes observed during repletion in patients with and without cancer.

Individual Case Summaries

In Tables I and II the primary measurements made in each patient are recorded. From these data the total circulating plasma proteins and hemoglobin may be directly calculated.

TABLE II

Primary Measurements in Cancer Patients During Repletion*

Patient age, % wt. loss	Time (days)	Body wt. kg	Alb.	Glob.	Hb	PV	RCV	Accumulated N balance g
5. J. L. (male)	0	63.2	3.7	2.5	12.3	3,320	2,220	0
64	27	65.9	3.4	2.1	12.2	3,500	2,140	302
13%								
6. E. C. (female)	0	39.2	2.7	2.6	14.7	2,740	2,165	0
56	13	39.5	2.7	2.6	15.1	2,380	1,995	
24%	19	38.3	2.7	2.7	14.1	2,605	1,975	285
7. M. H. (female)	0	34.5	2.7	3.4	9.0	2,855	1,105	0
38	12	34.3	2.7	3.4	10.6	2,925	1,125	
34	29	33.8	4.0	1.8	8.5	2,535	925	194
8. C. M. (female)	0	31.2	2.8	2.3	7.2	2,600	875	0
52	13	33.4	2.3	3.2	6.6	2,970	945	
45	44	36.2	2.3	4.3	7.9	2,640	1,065	216

* Key—same as in Table I.

In calculating expected weight gain from positive nitrogen balance, it is assumed that each gram of retained nitrogen is equivalent to 30 g of wet muscle tissue. This is based on the fact that 6.25 g of protein contain one g of nitrogen, and that five g of wet muscle contain one g of protein.

A. Non-cancer patients

Case 1. Malnutrition after severe head injury (Table I).

This patient sustained a severe head injury as well

as other soft tissue injuries in a street fight. He remained semi-comatose for five weeks, and an infected decubitus ulcer contributed to his protein losses. His normal body weight was 52.2 kg; the loss at the start of the study was 19 per cent thereof.

On an average daily caloric intake of 4,110 including 247 grams of protein for 27 days, the patient retained 478 g of nitrogen, or an average of 17.7 g per day. From the data presented in Table I, one may easily calculate the total circulating plasma protein and hemoglobin. Despite the marked nitrogen gain, there was no significant change in the total of circulating proteins (plasma protein plus hemoglobin) in this period. At the same time, the weight gain of 5.0 kg was considerably less than the expected gain (N x 30) of 14.3 kg.

The patient then left the hospital on a diet of his own choice for 82 days. When he returned for further study he had gained an added 5.4 kg in body weight, 24 g of serum albumin, 182 g of hemoglobin, 425 ml in red cell volume, 435 ml of plasma.

Comment: It is notable that the plasma albumin concentration was normal at the onset despite obvious tissue depletion. The patient demonstrated an apparent early preferential tissue protein need during the first month of repletion with a considerable gain in weight and little change in total circulating proteins. On an ad libitum diet thereafter, weight gain proceeded at about one-third the previous rate and with obvious gain in adipose tissue, but with appreciable gains in total circulating albumin and hemoglobin. These gains in circulating proteins are reflected in changes in concentration.

Case 2. Malnutrition due to fracture of the mandible (Table I).

This patient lost 33 per cent of a normal body weight of 60.0 kg after a fracture of the mandible complicated with infection. Thereafter he was provided with an average daily caloric intake of 3,240, containing 195 g of protein (31.2 g of nitrogen), and retained 486 g of nitrogen for 30 days, an average of 16.2 g a day. During this period, total circulating albumin gained was 13.0 g with a loss of globulin of 20 g. Plasma volume declined 240 ml. A substantial gain of 224 g of total circulating hemoglobin took place, coupled with a gain of 630 ml in red cell volume, and hemoglobin concentration improved appreciably. Actual weight gain was 4.5 kg (expected 14.6 kg). For the succeeding 17 days the patient was provided a hospital diet ad libitum with little change in circulating proteins and body weight.

Comment: In contrast to Case 1, plasma albumin and hemoglobin showed early gains during repletion. This pattern will also be observed in the two following non-cancer patients. The increment in red cell volume with a small fall in plasma volume has been observed in other studies[4] and will be discussed further. As noted in Case 1, the rate of weight gain was markedly reduced during the period of *ad libitum* diet.

Case 3. Malnutrition; arteriosclerotic heart disease; corrected cardiac decompensation (Table I).

This patient apparently became malnourished largely through neglect and economic embarrassment. He suffered from cardiac decompensation on admission, which may have contributed to his malnutrition. After digitalization and thorough diuresis, his depleted body weight was apparent and represented about 19 per cent of usual body weight of 54.5 kg.

Provided with an average daily intake of 2,630 cal, including 163 g of protein (26.1 g of nitrogen), the patient retained 288 g of nitrogen, an average of 10.3 g a day, for 28 days. He gained 3.6 kg in body weight. There was a remarkable gain of 1080 ml in plasma volume. This seemed at first a reflection of abnormal retention of fluid, but there were no signs of edema or decompensation. That the patient was actually dehydrated through vigorous cardiac therapy before repletion is also possible. In any case, with the increase in plasma volume, plasma protein concentration fell somewhat, although total circulating plasma protein increased by 53 g of which 34 g were albumin. Concomitant gains in red cell volume were 90 ml, and in total circulating hemoglobin, 115 g. The gain in body weight was 3.6 kg (expected 8.6 kg). During the next 44 days the patient was provided the hospital diet ad libitum with little change in circulating proteins and no change in weight.

Comment: This patient apparently made a rapid and fairly thorough restoration of circulating proteins during the first month of observation, although only 8.7 per cent of the total nitrogen retained was accounted for by gains in circulating proteins. The remainder was necessarily deposited as tissue protein. Thereafter on an ad libitum hospital diet for 6 weeks, there was no change in weight and little change in total circulating proteins.

Case 4. Malnutrition due to healed pyelonephritis (Table I).

This patient developed a severe pyelonephritis after a transurethal resection, accompanied by vomiting, fever and chills. His infection was finally brought under control and at this point his deficit in body weight was found to represent 38 per cent of his usual weight of 72.8 kg. With complete subsidence of the infection,

repletion was started with an average daily intake of 3,330 cal (as much as 5,000 cal on some days) containing 199 g of protein (31.9 g of nitrogen). The initial intake was less than the average for the entire period, for as appetite increased with repletion, the intake became larger. During the first 32 days he retained 446 g of nitrogen, or a daily average of 13.9 g. He gained 6.8 kg in body weight (expected 13.4 kg). Gains in total circulating hemoglobin (194 g), albumin (25 g), red cell volume (660 ml), and plasma volume (325 ml) were appreciable. Nitrogen balance studies were continued for 74 more days or a total of 106 days. The overall average retention of nitrogen was 15.2 g per day for this entire period of study. During the 106 days he manufactured 299 g of hemoglobin plus 69 g of plasma protein (36 g of albumin) which, however, represented only 3.7 per cent of the total nitrogen retained. Total gain in red cell volume was 1120 ml (more than a 100 per cent increase) while plasma volume increased only 395 ml.

On an ad libitum hospital diet for 20 more days, he gained only 1.8 kg in body weight while both the plasma volume and total circulating plasma proteins actually fell. Of the latter, however, the gain in albumin was sustained, while total circulating globulin fell 56 g. The red cell volume and total circulating hemoglobin fell slightly.

Comment: This patient represents the most depleted subject of this group both in total and in percentage weight loss. In addition, the long-standing renal infection had apparently produced a disproportionately large deficit in total circulating hemoglobin, red cell volume, and plasma proteins. As a result, for 106 days a gain in nitrogen and body weight was sustained, together with consistent gains in circulating albumin and hemoglobin. Of special interest was the striking improvement in appetite as repletion progressed so that increasingly greater caloric intakes were required for satiety. Only when ad libitum hospital diet was instituted after 106 days of uniform feeding mixtures did the rate of weight gain decline.

{B.} Cancer Patients:

Case 5. Adenocarcinoma of the rectum, resected, with generalized metastases (Table II).

This patient returned two and one-half years after an abdominoperineal resection of the rectum for cancer. Peripheral metastatic lymphadenopathy and a weight loss of 10 kg (13 per cent of normal body weight of 73 kg) had recently developed. On an average daily intake of 3,160 cal containing 190 g of protein (30.5 g of nitrogen) for a period of 27 days, he retained 302 g of protein, or an average of 11.2 g a day. His weight increased 2.7 kg (expected 9.0 kg). There was no appreciable change in his circulating proteins. Clinical evidence of rapid tumor growth was shown by rapid increase in the size of the involved peripheral lymph nodes. The patient went downhill rapidly as soon as hyperalimentation was discontinued and expired shortly thereafter.

Comment: In spite of weight gain, there was complete failure in the manufacture of circulating proteins. Perhaps the retained nitrogen was used exclusively by the metastatic cancer cells.

Case 6. Carcinoma of the esophagus, non-resectable (Table II).

This patient with non-resectable carcinoma of the esophagus was markedly depleted and had lost 24 per cent of her normal body weight of 51 kg, when repletion therapy was undertaken. On an average daily intake of 2,580 cal containing 153 grams of protein (24.5 g of nitrogen) for 19 days, she retained 285 grams of nitrogen, an average of 15.0 g a day. Nevertheless, she lost 0.9 kg in body weight (expected gain 8.5 kg). She also lost 76 g of circulating hemoglobin.

Comment: This case represents a complete failure of hyperalimentation as shown by failure of weight gain or gain in circulating proteins. The patient expired three days after the study was discontinued.

Case 7. Carcinoma of cervix, post-radiation persistence (Table II).

This patient with a persistent carcinoma of the cervix despite radiation therapy had lost 34 per cent of her normal body weight of 52.2 kg. On an intake of 1,820 cal average per day, containing 120 g of protein (19.1 g of nitrogen) for 29 days, she retained 194 g of nitrogen, or a daily average of 6.7 g. While she lost 0.8 kg in body weight, there was a surprising gain of 25 g of albumin even though plasma volume declined 320 ml. Low grade bleeding for the last 10 days contributed somewhat to a loss of 62 g of hemoglobin. The patient died six weeks after this study was discontinued.

Comment: This patient represents the only instance in which a patient with cancer has shown a favorable response in albumin manufacture, although total globulin losses were greater than albumin gains.

Case 8. Carcinoma of the breast, postoperative persistence (Table II).

This patient developed massive carcinomatous involvement of the right breast and axilla after a left radical mastectomy. At the time of repletion studies, she had lost 45 per cent of her normal body weight of 56.8 kg. For 44 days on an average intake of 2,270 cal, including 126 g of protein (20.1 g of nitrogen) she

retained 216 g of nitrogen, an average of 4.9 g a day. The weight gain was 5.0 kg (expected 6.5 kg). A gain in total plasma protein of 41 g was offset by a loss of 12 g in albumin. This patient died one month after hyperalimentation was discontinued.

Comment: Again one notes no favorable effect on albumin and hemoglobin manufacture, in spite of a significant gain in weight.

The above findings are now summarized as follows in terms of: (A) initial values; (B) nitrogen balance and weight gain; (C) changes in blood volumes and total circulating proteins.

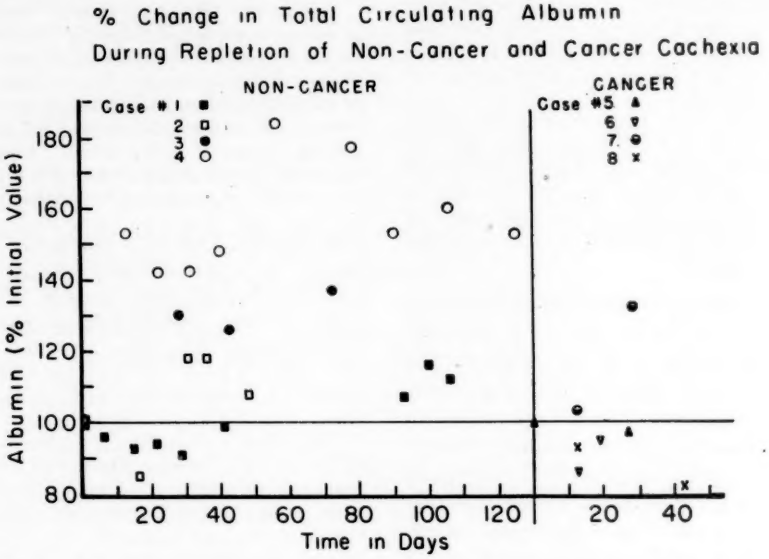

Fig. 1. Note the consistent gain in total circulating albumin during repletion in non-cancer patients, in contrast to essentially no change in the cancer group. Case 1 varied from the usual pattern in that there was no gain in total albumin until later, due perhaps to a relatively high value at the onset (see text).

(A) *Initial Values:* From data presented in the two tables, one may calculate the initial plasma and red cell volumes in ml/kg of body weight. Plasma volume varied from 57 to 75 ml/kg, and red cell volume from 23 to 43 ml/kg in non-cancer patients. The lowest red cell volume was found in the patient with the healed kidney infection. In cancer patients, plasma volume was 53 to 84 ml/kg and red cell volume 28 to 57 ml/kg. Thus the plasma volume in both groups based on body weight was considerably greater than the commonly accepted average of 45 ml/kg[22] and higher even than we have observed in normal but exceptionally lean individuals.[23] The red cell volumes in non-cancer cachexia, on the other hand, were unchanged from the reported average of 40 ml/kg[22] and were even slightly greater than our own observations in normal patients, except in Case 4, in which chronic infection was present prior to repletion. In cancer patients, however, the red cell volume was considerably lower. All values would have been lower, of course, if calculated on the basis of usual or ideal weight as is frequently done.[24]

A notable exception was Case 6, a patient with cancer of the esophagus, with a red cell volume of 57 ml/kg. This remarkably high value was confirmed in repeated measurements during the period of study and was not due to dehydration.

(*B*) *Nitrogen Balance and Weight Gain:* In non-cancer cachexia during repletion, nitrogen balance was always positive, averaging 10 to 18 g a day, representing about 45 per cent of the intake.

The consistent weight gains, however, were not proportional to the nitrogen gain if one as-

sumes that each gram of retained nitrogen is synthesized to 30 g of wet muscle tissue.[25–27] The per cent of nitrogen gain accounted for by gains in circulating proteins (plasma and hemoglobin) for periods of about one month was small, varying from zero to 8.7 (Case 4, 106 days, 3.7 per cent).

In the cancer patients, nitrogen balance, though consistently positive, was less in degree than in non-cancer patients, due partly to the smaller intake. Weight gain was variable, but again less than in non-cancer patients.

pense of a loss in globulin, were observed in non-cancer patients, but not in cancer patients. The average gain in albumin in non-cancer patients during the first month of repletion represents 18 per cent of the initial value, while simultaneously there was an 11 per cent gain in body weight.

The average gains in red cell volume and hemoglobin in non-cancer patients represent 27 per cent of initial values, more than twice the percentage gain in weight for one month. The absolute red cell volume and total circulating

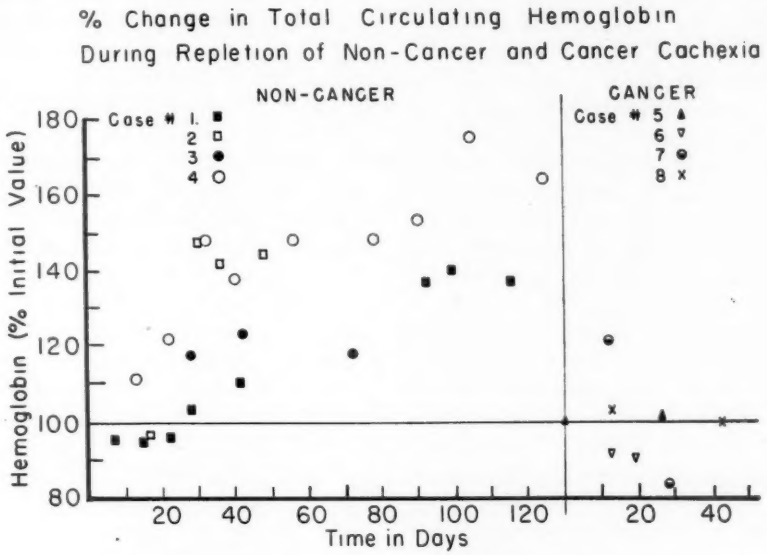

Fig. 2. Note that the gains in total circulating hemoglobin during repletion of non-cancer patients is seen to follow an almost linear progression proportionate to the repletion time. Cancer patients, on the other hand, show no significant increments in total circulating hemoglobin.

(*C*). *Changes in Blood Volumes and Total Circulating Proteins:* There were rarely significant changes in absolute plasma volume during repletion, although the high initial figure per kg of body weight fell because of weight gain. An exception was Case 3, a patient who had recovered from an episode of cardiac failure and whose plasma volume increased by 1080 ml as already discussed.

Total circulating plasma proteins likewise did not change appreciably during repletion of both groups of patients. However, significant gains in total circulating *albumin*, largely at the expense of a loss in globulin, were observed in non-cancer patients, but not in cancer patients. The average gain in albumin in non-cancer patients during the first month of repletion represents 18 per cent of the initial value, while simultaneously there was an 11 per cent gain in body weight.

The average gains in red cell volume and hemoglobin in non-cancer patients represent 27 per cent of initial values, more than twice the percentage gain in weight for one month. The absolute red cell volume and total circulating hemoglobin of non-cancer patients showed a consistent increase even though it was slow, requiring 6 to 18 weeks before expected values based on usual weight were approached. It is probable that restoration is not fully achieved until the usual body weight is regained. The cancer patients, on the other hand, demonstrated no significant changes in red cell volume or total circulating hemoglobin.

Scatter diagrams (Figs. 1 and 2) depict the percentage change in total circulating albumin and hemoglobin during repletion in non-cancer and cancer patients. The number of points

above the baseline (100 per cent = initial value) in the non-cancer group far exceeds the number below the baseline; in the cancer group this distribution is reversed, and the sum of points indicates no significant gain, or even a loss.

COMMENT

The large variation found in the initial values of plasma volume (expressed as ml/kg) in these depleted patients was one of the first characteristics noted in the findings reported herein. This variability may have been due, of course, to differences in the depleted state at the beginning of each study, due presumably to differences in the intake leading to malnutrition. That this is not necessarily the case is shown by scrutiny of the results of a controlled experimental study of depletion and repletion by Keys *et al.*,[5] in which uniform semi-starvation diets were provided. Absolute changes in plasma volume during 24 weeks of depletion in 32 cases varied from −457 ml to +836 ml although the average change was +264 ml. Similar variations were observed during repletion. Thus in 16 cases in which data are recorded, the absolute individual plasma volume changes during a 12-week repletion period varied from −1,384 to +339 ml. Some of this difference may have been due to differences in the repletion intake. Nevertheless, even within a single group on a uniform intake considerable variation was recorded. Thus in group T one subject (No. 108) actually lost 1,384 ml of plasma while another (No. 111) gained 251 ml. Obviously there must be certain factors in each individual to account for these differences, of which the pituitary-adrenal response to starvation and repletion may be one. In any case, these as yet indeterminate factors must be reckoned with and may account for the many variations we also observed.

Significant too was the observation that initial plasma volumes in our depleted patients in terms of ml/kg were all higher than usually reported by others.[10,24,28] The reason is partly due to the fact that we have used the depleted body weight as a basis of calculation in contrast to the usual or normal body weight commonly employed. Yet even based on usual body weights, the initial plasma volumes in our patients would be slightly elevated, which is in accord with most of the controlled observations on depletion of Keys in experimental depletion.

In contrast to the elevated initial plasma volume in depleted patients, the initial red cell volume and total circulating hemoglobin were at average normal or decreased levels. On the basis of usual body weight they were uniformly low, indicating a greater loss of hemoglobin and red cell volume than plasma protein and plasma volume under the conditions of human starvation observed in our patients. Disproportionately large deficits were seen in the presence of chronic infection and cancer. All but one of the subjects studied by Keys *et al.* demonstrated a loss of red cell volume during depletion.

Noteworthy in the present study is the failure to gain as much body weight during repletion as might be expected by the high degree of nitrogen gain. The same phenomenon has also been observed by others in both cancer and non-cancer cachexia.[1,15,16] This discrepancy was more pronounced in two cancer patients in whom there was even some loss of weight despite positive nitrogen balance. The behavior of water may explain this phenomenon. Thus the water, which makes up approximately 80 per cent of the weight of the muscle mass, may be derived in part from a shift of extracellular to the intracellular water during the process of tissue protein repletion. If this be the case, tissue protein could be deposited without the expected change in body weight. It is well known that early in the course of repletion of extremely malnourished patients the body weight may fall due to loss of edema. This is obvious when edema is clinically evident, but the extracellular space may be abnormally large in the absence of clinical edema. Loss of the water then is often evident by diuresis if measured. In the present studies diuresis and a transient fall in body weight were not observed. It is clear that further and more exact studies of total body water and particularly the relationship between intra- and extracellular water is necessary.

The rate of gain of weight in the non-cancer patients was most rapid during the first month of repletion in the first three patients. A fall

in the rate of weight gain took place thereafter which was evidently due either to the fact that essential restoration of the accrued nitrogen deficit had been accomplished, or to the change to a hospital diet. In Case 4, with the most severe depletion, weight gain was consistent on the uniform feeding mixture, at a steady rate for three and one-half months. When intake was shifted to a hospital diet, the rate of weight gain declined. Very probably then, the feeding mixture, providing a known high caloric and protein intake, was largely influential in determining the rate of weight gain.

The relatively small changes in total circulating plasma proteins and plasma volume during repletion of non-cancer patients is somewhat misleading in view of significant gains in total circulating albumin. Thus the gain in albumin was usually proportionately greater than the gain in body weight. An actual loss in globulin accounts for the small changes in total plasma protein observed. On the other hand, the cancer patients failed to gain either total plasma protein or albumin. The one exception, Case 7, with a gain of 25 g of albumin, exhibited low grade bleeding during the last ten days of study. This may be significant in that hemorrhage is known to provoke the regeneration of albumin.[29]

Of interest, in those non-cancer patients who manufactured albumin during repletion, was the gain expressed as a percent of the total nitrogen retained. Calculations reveal figures of 0.43 to 1.89 per cent, which are lower than the 2 to 4 per cent observed by Sacher *et al.*[30] in experiments on repletion of dogs. However, in these experiments the plasma volume was not measured but was assumed to represent 5 per cent of the body weight at all times. This may explain the discrepancy.

The changes in circulating hemoglobin were more pronounced than those in the circulating plasma protein; this would indicate that hemoglobin is lost and gained more readily than plasma protein, a finding also noted in the observations of Keys *et al.*

Of interest in Case 1 (non-cancer) is the absence of a gain in circulating albumin and hemoglobin during the first month of study, unlike the increase in the other three cases. This may be due to the relatively high initial albumin concentration. However, the delay in hemoglobin manufacture is not easily explained except as a manifestation of preferential tissue protein regeneration. Generally both albumin and hemoglobin increased during the period of administration of the feeding mixture.

The failure of hemoglobin regeneration in cancer as compared with non-cancer cachexia was striking. While nutritional intake in the cancer patients was somewhat smaller, this would not seem to explain the failure of albumin and hemoglobin regeneration. Other factors including the presence and growth of the tumor must be considered.

It should be noted that the four patients with cancer proved somewhat by chance to be suffering from extremely advanced disease, for all died within three days to six weeks after observations were discontinued. It may be that the advanced stage of the cancer in these four patients is an important factor in their failure to manufacture albumin or hemoglobin in spite of positive nitrogen balance in all and weight gain in two. The more favorable clinical response in patients with cancer undergoing repletion reported previously[2] is undoubtedly due to the fact that the disease was less advanced. Changes in total circulating albumin and hemoglobin during longer periods of repletion are being studied in similar patients, in whom the cancer is not quite so close to its terminal stage.

SUMMARY

Based on the depleted body weight, initial plasma volume in cachexia is high without a corresponding change in red cell volume. The individual variations were great but no greater than those found by others.

During repletion (hyperalimentation) gain in weight and in total circulating albumin and hemoglobin was most pronounced in non-cancer cachexia as long as a high caloric and protein intake was provided with a uniform feeding mixture as the sole nutritional intake. On subsequent *ad libitum* hospital or out-patient diets, repletion was less evident for periods up to one month.

In four advanced cases of cancer cachexia, weight gain was consistent but there was a striking failure in regeneration of plasma albumin and hemoglobin.

In non-cancer cachexia in the absence of hemorrhage, the manufacture of plasma albumin and hemoglobin tends to proceed at the same rate as weight gain, or even more rapidly. Plasma globulin varied widely and is of little significance as a measure of the nutritional state or of repletion.

Overall gains in circulating plasma albumin plus hemoglobin for 27 to 106 days accounted for only a small amount (not greater than 8.7 per cent) of the total nitrogen retained during repletion. The maximum gain in albumin was 1.89 per cent of the total nitrogen retained.

Despite great and inevitable individual variations during hyperalimentation in non-cancer cachexia, positive nitrogen balance was consistently greater than can be accounted for by observed gain in body weight and total circulating hemoglobin and plasma protein. A shift in body water from the extracellular to the intracellular space could account for this discrepancy.

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Do Vegetables Make Bones?

"One farmer says to me, 'You cannot live on vegetable food solely, for it furnishes nothing to make bones with'; and so he religiously devotes a part of his day to supplying his system with the raw material of bones, walking all the while he talks behind his oxen, which, with vegetable-made bones jerk him and his lumbering plow along in spite of every obstacle."

—Henry David Thoreau in "*Walden*" (Modern Library Ed., p. 8).

Lysine, Threonine and Other Amino Acids as Supplements to Rice Diets in Man: Amino Acid Imbalance

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With the Technical Assistance of HOWARD BAKERMAN, B.S., ROBERT ING, B.S., JOHN THOMAS, B.S., AND JEAN CURRAN, B.S.

PECORA and Hundley[1] found that supplements of lysine and threonine improved the biologic value of rice for the growing rat. An unusual feature was that neither lysine nor threonine alone was effective, while both together increased growth approximately three fold. These results have been confirmed and extended by investigators at the University of Wisconsin[2,3] who also found in growing rats that amino acid supplements may have undesirable effects unless the amino acids are properly balanced. Kik[4] has found that lysine and threonine improve protein efficiency with both whole and milled rice diets. In other animal experiments Sure[5] recently reported an additional supplementary value of methionine in lysine and threonine supplemented milled rice diets. Others,[1,2] however, have not observed any beneficial effect of methionine in such diets.

The primary purpose of the present experiments was to determine whether lysine and threonine would improve the biologic value of rice for *man*. Other amino acid mixtures were tested to control the effect of varying nitrogen intakes and to explore further the ability of amino acid supplements to improve the utilization of rice protein. Nitrogen balance was the primary technic used.

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† Deceased.

METHODS AND PATIENTS

The general plan was to maintain subjects on rice-fruit diets which contained rice (250 or 350 g), fat (100 g), fruit and sugar to provide 4.31 to 5.07 g of N and 2,800 to 3,500 calories daily. Eighteen to 30 days were allowed for "adjustment" to the experimental diet, following which an amino acid mixture was added for 12 or more days. Several amino acid mixtures were evaluated in the same subject with periods on the unsupplemented diet interspersed so that amino acid effects could be evaluated against pre- and post-control periods. In all but one of the subjects a normal (control) 85 g protein diet with the same caloric content as the rice-fruit diets was used for one to three metabolic periods at the beginning and at the end of each experiment.

The subjects were four normal young adult male volunteers. One subject was used in two separate experiments (see Table I). They were maintained on a metabolic ward under close supervision. Normal physical activity was permitted and encouraged although unusually vigorous exercise was not permitted. Cooperation was excellent and at no time were irregularities in food consumption suspected or detected. Urine was refrigerated without preservative immediately after each voiding and collected to provide 24-hour specimens. Stools were refrigerated immediately after collection. Six-day metabolic periods were used with 0.4 g carmine given orally as the stool marker. Stools were prepared for analysis by the "dry"

method.[6] Twenty-four-hour urines and the six-day stool pools were analyzed for nitrogen by a modification of the Kjeldahl method[7] and urines for creatinine by the method of Folin.[8] In four of the subjects the daily urinary excretion of arginine, lysine, and threonine was determined on the last two consecutive days of each metabolic period. Urines were hydrolyzed and concentrated essentially as described by Ulrich.[9] In three of the subjects, arginine, lysine, and threonine were determined (once in each metabolic period) in whole serum and on precipitated serum proteins derived from fasting blood. Serum proteins were precipitated with 10 volumes of 5 per cent trichloroacetic acid and collected on filter paper. Whole serum and precipitated serum proteins were hydrolyzed in 2.5 N NCl by autoclaving 10 hours at 15 lb pressure. The hydrolyzates were neutralized with sodium acetate and NaOH, filtered, ethyl ether extracted and diluted to volume. All amino acid analyses were performed microbiologically, lysine according to Horn *et al.*,[10] arginine and threonine as described by Barton-Wright.[11] Hemoglobin, hematocrit, total serum proteins, A-G ratios, and blood urea nitrogens were determined weekly by standard clinical laboratory procedures.

Body weights were recorded daily. Basal metabolic rates were determined periodically in most of the subjects. Three of the subjects received daily dynamometer tests for strength in each hand and a pull test for pectoral strength.

DIETS

The diets used for each subject are summarized in Table I. Three meals per day were prepared from weighed ingredients using two menus virtually identical in calorie and protein content which were alternated successively to provide a "constant" protein, fat and calorie intake at the selected level. The protein, fat, and calorie content of foods used were calculated from standard food composition tables.[12] Metabolic kitchen methods were used which permitted no loss of any of the constituents being measured.[13] Foods were purchased in bulk lots to reduce variation in composition. The four lots of rice used in these studies had an actual N content ranging from 0.96 to 1.19 per cent based on the average of duplicate Kjeldahl determinations.* However, the values presented in Table I and all other calculations in this paper assume the N content of rice to be 1.2 per cent. Since the experiment involved assessment of changes in N balance rather than absolute balance, this procedure is thought to be valid. A record was kept of the lots of rice used. Changing from one to another lot of rice with a slightly different N content could not have influenced the results except on one occasion to be mentioned later. Rice was divided in equal amounts for each meal and prepared in any fashion desired within the limitations of the foods allowed; considerable variety was obtained through dietetic manipulation. Salt and other condiments were not restricted. The only animal protein came from the 0.6 g of milk protein found in 100 g of butter or margarine. Each subject received a vitamin capsule daily, Novogran® and Theragran® (Squibb) being alternated.

* We are indebted to Dr. W. C. Alford and his associates in the Microanalytical Laboratory, National Institutes of Health, for these analyses.

TABLE I

Proximate Composition of Rice-Fruit Diets

Subject	Protein g	Fat g	Carbohydrate g	Cal	Cal/kg body wt	Rice g	Total diet N g	% N from rice
W. M.	26.0	100	450	2,800	47	250	4.31	70
V. L.	26.0	100	450	2,800	39	250	4.31	70
R. B.	26.0	100	450	2,800	41	250	4.31	70
W. Y.*	28.8	100	625	3,500	50	250	4.61	65
W. Y.*	31.7	100	500	3,000	36	350	5.07	83

* This subject was used in two separate experiments.

TABLE II

Nitrogen Balance by Metabolic Periods

Period	W. M. Diet	W. M. Supplement	W. M. N balance, av. g/day	W. M. S.E.	V. L. Diet	V. L. Supplement	V. L. N balance, av. g/day	V. L. S.E.	R. B. Diet	R. B. Supplement	R. B. N balance, av. g/day	R. B. S.E.	W. Y. (3,500 cal) Diet	W. Y. (3,500 cal) Supplement	W. Y. (3,500 cal) N balance, av. g/day	W. Y. (3,500 cal) S.E.	W. Y. (3,000 cal) Diet	W. Y. (3,000 cal) Supplement	W. Y. (3,000 cal) N balance, av. g/day	W. Y. (3,000 cal) S.E.
1	Control		+0.73		Control		−1.76		Control		+1.04		Control		+0.35		Basal rice		−4.40	
2	"		+0.94		"		−0.81		"		+0.64		"		+2.45		"		−1.42	0.09
3	"		−0.10		"		−0.85		Rice	TLM	−2.38		Basal rice		−2.26		"		−0.79	
4	Basal rice		−1.96	0.85	Basal rice		−3.48		"	TLM	−1.01	0.13	"		−1.93		"	L	−0.51	0.07*
5	"		−0.50	0.09	"		−1.38	0.12	"	TLM	−1.34		"		−1.35		"	L	−0.73	
6	"		−1.01		"		−1.81		"	EAA#3	−0.85	0.18	"		−1.35	0.09	"		−0.91	0.07
7	"	TL	−0.13	0.07*	"	TL	−1.26	0.06	"	EAA#3	−0.25*		"		−1.23		"		−1.27	
8	"	TL	−0.12		"	TL	−1.19		"		−0.58	0.09	"	LTH	−1.11	0.15	"	TL	−0.47	0.09*
9	"	TL	+0.47		"	TL	−1.05		"		−0.66		"	LTH	−0.68*	0.14	"	TL	−0.54	
10	"	TLM	+0.21	0.15	"	TLM	−0.55	0.09*	"	NEAA	+0.17	0.15*	"		−1.36	0.13	"		−0.66	0.07
11	"	TLM	+0.22		"	TLM	−0.28		"	NEAA	−0.31		"		−0.74		"		−0.77	
12	"		+0.21	0.08	"		−0.76	0.06	"	TL	−0.27	0.08	"	EAA#6	−0.14	0.10*	"	T	−0.92	0.13
13	"		0.0		"		−0.52		"	TL	+0.04		"	EAA#6	+0.13		"	T	−0.40	
14	"	NEAA	+0.73	0.11*	"	EAA#3	−0.37	0.20	"		−0.17	0.11	"		−0.63	0.10	"		−0.68	0.14
15	"	NEAA	+0.42		"	EAA#3	−1.41†		"		0.0		"		−0.26		"		−1.22	
16	Control		+5.19		Control		+3.27		Control		+5.76		"	TL	−1.08	0.08†	"	NEAA#9	−0.63	0.09
17	"		+2.64		"		+2.11		"		+4.76		"	TL	−0.98		"	NEAA#9	−0.83	
18													"		−0.25	0.22	"		−0.80	0.20
19													Control		+5.24					

Control = 85 g protein normal diet at same caloric intake as the basal rice diets.
S.E. = Standard error of the mean for the periods indicated.
* = Significant shift toward positive N balance.
† = Significant shift toward negative N balance.

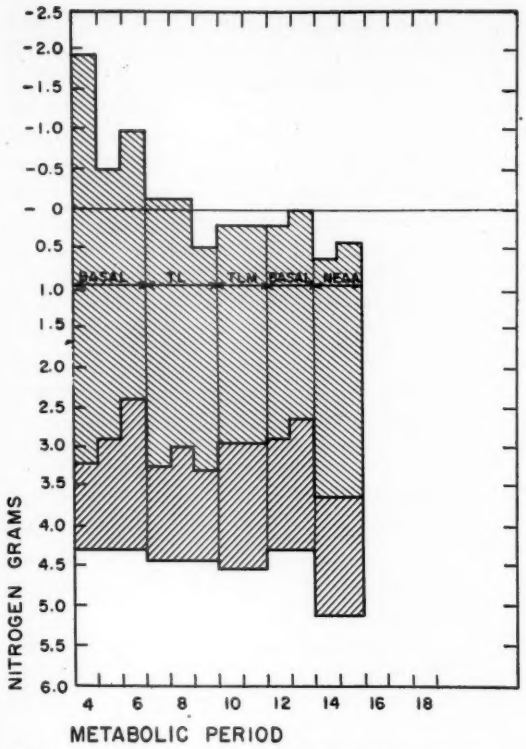

Fig. 1. Subject W. M.: Metabolic periods are six days each. The data are plotted as average 24-hour values for each period. Periods 1–3 and 16–17 (not shown) were on the control 85 g protein diet (see Table II). N intake is plotted from the zero line to the bottom of the shaded area. The lower shaded area is stool N; the upper shaded area is urinary N. Shaded areas above the zero line represent negative N balance, open areas below the zero line represent positive balance.

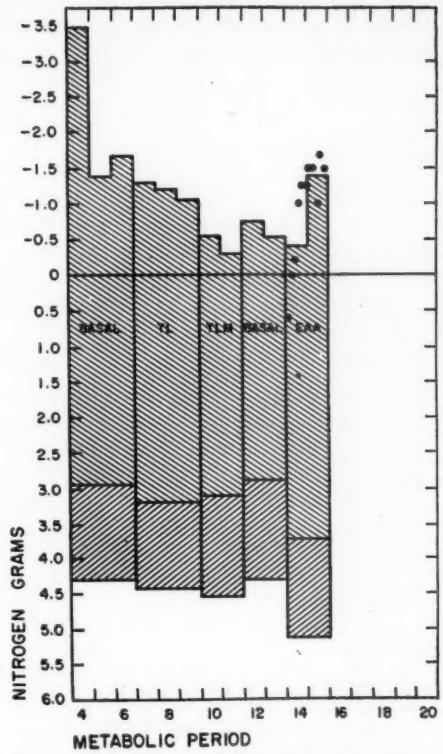

Fig. 2. Subject V. L.: The method of data presentation is the same as described under Figure 1. The black dots in periods 14 and 15 indicate daily N balance.

AMINO ACID SUPPLEMENTS

One third of the daily amino acid supplement was mixed with the cooked rice served at each meal. The amino acid mixtures used are identified by symbols as follows: TL (or LT) = L-threonine 0.38 plus L-lysine* 0.62 g daily (0.14 g N); T or L used alone = 0.62 g daily of the indicated amino acid (0.073 or 0.095 g N, respectively); TLM = TL plus DL-methionine 1.0 g (total N = 0.234 g); LTH = TL plus L-histidine HCl 0.6 g (total N = 0.26 g); EAA #3 = a mixture of the 8 essential amino acids in Rose's "minimum" amounts[14] except for T and L which were present in the same amount as in the TL mixture (total of 0.82 g N daily); EAA #6 = the same as EAA #3 except T and L also were present at Rose's "minimum" (0.92 g N daily); NEAA = non-essential amino acids, glycine 0.94, DL-alanine 1.12, L-glutamic acid 1.84, DL-aspartic acid 1.67, and L-histidine HCl 0.60 g, the mixture being equal in total nitrogen to EAA #3; NEAA #9 = glycine 0.15 plus L-glutamic acid 0.47 g, the mixture being isonitrogenous with 0.62 g of L-threonine, and almost isonitrogenous with the same amount of L-lysine.

The statistical significance of changes in N balance was obtained from the average of daily N balance data for 6, 12, or 18-day experimental periods. Standard errors for 6- and 12-day periods were calculated using the method of

* The lysine used in this and all other supplements was L-lysine HCl, 95 per cent grade.

Mantel[15] and for 18-day periods by the conventional method. Fisher's table of t values[16] and the formula $t = \frac{M_1 - M_2}{\sqrt{SE_1^2 + SE_2^2}}$ were used to obtain p values.

RESULTS

As shown in Table II, the change from the control diet providing 85 g of protein to the rice diets providing 26–31.7 g of protein resulted in markedly negative balances, followed by a trend toward zero balance with time as has been observed by others using similar diets.[17–19] A conventional plot of nitrogen balance for the subject who adjusted most rapidly is shown in Figure 1, while two subjects who showed less complete adjustment are depicted in Figures 2 and 3. No clear relationship between level of caloric intake and the speed of this adjustment was apparent. One subject (W. Y.) did not adjust more rapidly with 350 g of rice daily (3,000 cal) than he did with 250 g of rice (3,500 cal) in a separate experiment.

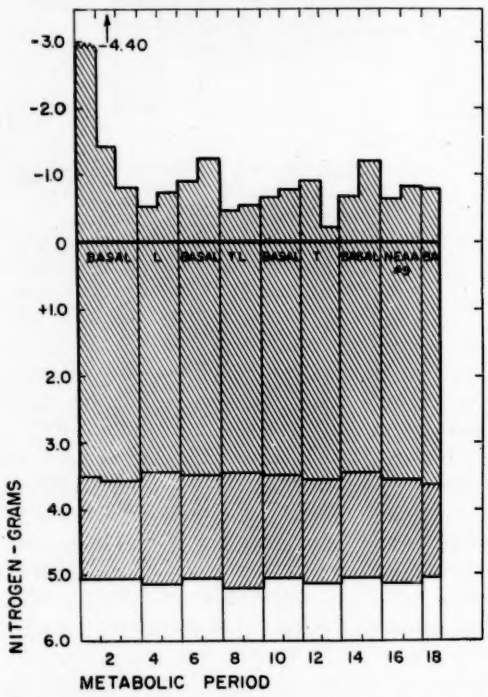

Fig. 3. Subject W. Y.: (3,000 cal, 350 g rice experiment): Data plotted as described under Figure 1.

These facts made it clear that amino acid effects would have to be evaluated against (1) pre- and (2) post-basal diet periods as well as (3) the apparent trend of "adjustment" between periods on the unsupplemented basal diet. A result was not considered clear unless the differences in at least two out of three of these comparisons were significant at $p = 0.01$ or less. In general a shift in N balance equal to at least 7 per cent of N intake was required before such statistical significance could be demonstrated. Charts were constructed to estimate the probable trend of adjustment as illustrated in Figures 4 and 5. These simplified charts permitted visualization and evaluation of "adjustment" trends.

Threonine and Lysine

The TL mixture was tested once in each subject. No uniform response was found. One subject, W. M. (Fig. 1), showed a highly significant shift toward positive balance. A second subject, W. Y. (Fig. 3), showed a highly significant positive response when the data were plotted using the assumed value of 1.2 per cent N for rice. However, it was necessary to change from a lot of rice having 1.19 per cent N to a lot having 0.96 per cent N at the beginning of metabolic period #8. When the data were recalculated using these values the TL response was present but not statistically significant. A third subject, R. B. (Fig. 5), showed no significant change with TL. However, N balance with TL was not significantly different than in the preceding two periods with NEAA, the latter result being significantly positive. This result also must be regarded as uncertain. A fourth subject, V. L. (Fig. 2), showed no response to TL, but did shift significantly toward positive balance when M was added to the TL mixture. The fifth subject, W. Y. (Fig. 4), showed a highly significant negative response to TL (designated LT in Figure 4). In the same experiment this subject had previously shown a small positive response to the TLH mixture which showed borderline statistical significance ($p = 0.02$) during period 9 (Fig. 4). There is no reason to believe that H exerted any specific influence in this mixture aside, perhaps, from its contri-

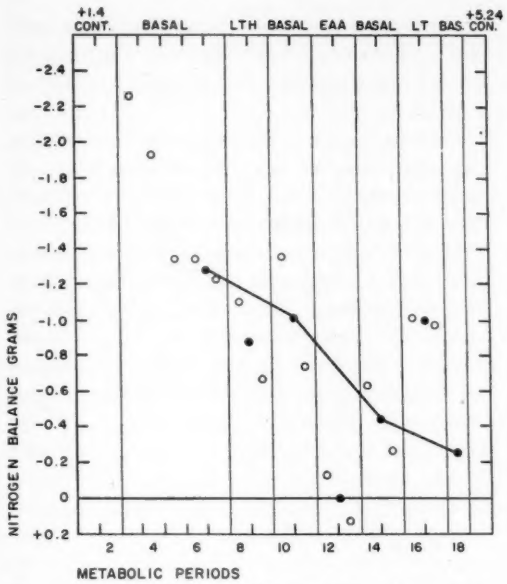

Fig. 4. Subject W. Y. (3,500 cal, 250 g rice experiment): Only N balance is plotted in this "trend" chart. The open circles represent average 24-hour values for one metabolic period. The black dots are the average of two consecutive periods (only one in the case of period 18). The heavy line connects periods on the unsupplemented basal diet.

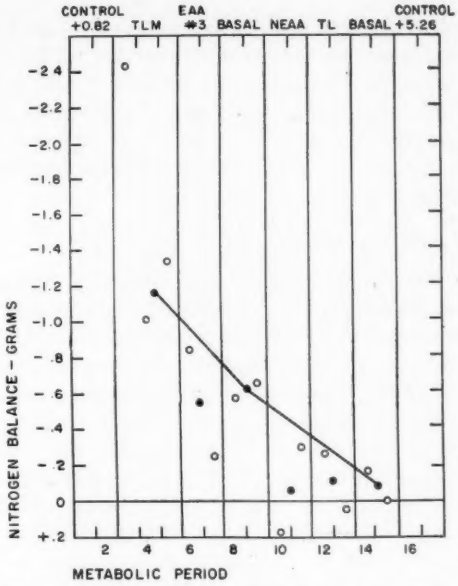

Fig. 5. Subject R. B.: A "trend" chart of N balance plotted as described under Fig. 4.

bution of N. Also, this same subject, in another experiment (Fig. 3), had shown a questionable positive response to TL, as mentioned above, and had shown a highly significant positive response to L alone.

Methionine

As mentioned above, the addition of M to the TL mixture induced a positive shift in N balance in one subject where TL alone was ineffective (Fig. 2). In another subject (Fig. 1) TLM was no more effective than TL alone, although this subject was in slight positive balance at the time. TLM was also used in one subject (Fig. 5) from the beginning of the rice-fruit diet in an effort to reduce the initial heavy nitrogen loss and speed the trend toward balance. No effect could be discerned.

The Essential Amino Acids

Mixtures of the eight essential amino acids were tested primarily to demonstrate the ability of supplemental amino acids to produce a positive shift in N balance and to obtain some idea of the magnitude of the shift from the eight essential amino acids in comparison to TL. EAA #6, the eight essentials in Rose's "minimum" amounts, resulted in a highly significant positive shift (Fig. 4), although the average balance for two periods was just zero, and the magnitude of the shift was not significantly better than with TL in one trial (Fig. 1). EAA #3, the same as #6 except for TL which was present in the same amounts as in the TL mixture, resulted in a definite but smaller positive shift (Fig. 5). However, in another subject (Fig. 2), EAA #3 caused a highly signicant negative response over the 12-day period. An examination of the daily N balances, plotted as solid black dots in Figure 2, makes it clear that this mixture produced an initial positive, followed by a stronger negative shift. No extraneous influence such as fever or diet irregularity could be found to account for this result.

Effects of Nitrogen

NEAA, a mixture of non-essential amino acids isonitrogenous with EAA #3, resulted in positive shifts in N balance (Figs. 1 and 5)

approximately equal to those from EAA #3 and TL in the same subjects. However, NEAA #9, approximately isonitrogenous with T and with L, resulted in no significant positive shift, as was the case with T alone. L alone however resulted in a highly significant positive shift (Fig. 3).

Other Observations

No subject reported any change in appetite or sense of well-being with addition or omission of amino acids (the subjects did not know when changes in diet supplements were made). Three subjects developed small aphthous ulcers which healed promptly. Otherwise there was no detectable change in general health. No changes in muscle strength tests were found. The diets became quite monotonous but all subjects consumed them with less difficulty than expected. Subject V. L. lost about 2 kg of body weight while on the rice-fruit diet. W. M. gained 1 kg, R. B. showed no change, W. Y. gained 6 kg while on the 3,500 cal diet, and lost 1.5 kg in the other experiment at 3,000 cal. W. M., who attained N balance most quickly, showed a drop in hemoglobin from 14.2 to 13.1 g, hematocrit from 48 to 38.5, total serum protein from 7.3 to a low of 5.8 g per 100 ml at which point there was a reversal of the A-G ratio. V. L. also showed a drop of about 1 g in hemoglobin and a corresponding drop in hematocrit although no change in serum proteins was found. R. B. and W. Y. showed no significant blood changes. Blood urea N dropped from 14 to 19 on a normal diet to 4 to 9 mg per 100 ml in subjects W. M., V. L., and R. B. while on the rice-fruit diets. This constituent was not followed in subject W. Y. No other changes in blood chemistry were noted. The 24-hour urinary excretion of creatinine ranged from 22 to 27 (average of 25) mg per kg body weight while on the normal control diet. These values decreased consistently in each subject to range from 18 to 21 mg per kg (19 to 30 per cent decreases) while on the rice-fruit diets. This decrease occurred irrespective of whether the subjects gained or lost weight during the experiment. Although the subject V. L who lost the most weight (2 kg) showed the greatest decrease (30 per cent), subject W. Y. showed a 19 per cent decrease in the experiment where he gained 6 kg body weight and a similar decrease in the experiment where he lost 1.5 kg.

There was no change in the per cent of arginine, lysine, or threonine in whole serum, or in serum proteins in the three subjects studied. The urinary excretion of arginine, lysine, and threonine in four subjects is summarized in Table III. There was a slight to marked drop in the excretion of these amino acids when the subjects changed from a normal (85 g protein) to the rice-fruit diets. Arginine declined least (rice is relatively rich in arginine), lysine most, with threonine intermediate. Urinary lysine and threonine were influenced very little by the presence or absence of these amino acids as dietary supplements. By the same token, it is clear that the supplemental amino acids were utilized in some fashion, since they were not spilled in the urine in appreciable amounts.

DISCUSSION

While several of the amino acid mixtures produced significant positive shifts in N balance, these effects, even of a mixture of the eight essential amino acids in "minimum" amounts, were considerably smaller than expected from the animal studies.[1–5] Positive balance was achieved in only a few instances and was very small when compared to the cumulative nitrogen deficit. Four of these subjects were placed on 85 g protein normal diets for one or two metabolic periods at the conclusion of the rice-fruit diet (calories were held constant). Each retained nitrogen avidly, positive balance varying from 2.9 to 5.26 g per day. This is in contrast to a positive balance of about 0.6 gm N, the greatest shown by any subject on the amino acid supplemented diets. Since these subjects obviously had the capacity to retain substantial nitrogen, it seems to follow that none of the amino acid-supplemented diets were particularly efficient with respect to nitrogen retention. In view of Rose's observation[20] that higher calorie levels are required when using amino acid mixtures, it was thought possible that the higher calorie levels used in some of our subjects might improve nitrogen utilization. This did not prove to be the case.

On the other hand, the positive shifts in N balance as a result of amino acid supplements in our experiment are in the same range as observed by Hegsted *et al.*[21] in adding lysine and methionine to all-vegetable diets. Certainly an amino acid supplement which would improve nitrogen utilization 7 to 12 per cent would have significance in long-term nutrition where protein is limited in quantity or quality. However, it must be noted that there is no assurance that either the positive or negative effects observed in our relatively short-term experiments would persist under conditions of long-term feeding. In addition, nitrogen balance is an indicator of only one aspect of nitrogen and protein metabolism.

However, our experiments did not yield evidence of a uniform pattern of response to the amino acid supplements used. The most significant part of our data would seem to be in demonstrating that amino acid supplements which have a favorable effect on nitrogen utilization may also have a distinctly unfavorable effect in certain situations. The importance of "amino acid balance" in nutrition has been discussed and reviewed elsewhere.[22] According to this concept, supplementation of a diet with amino acids which are not primarily limiting may increase the severity of the primary amino acid deficiency; or supplementation with the most limiting amino acid may precipitate a deficiency of the next most limiting amino acid; or, an excess of an amino acid may reduce the utilization of another amino acid, that is provided in normally adequate amounts, to such an extent that deficiency occurs.[22] There is a considerable body of data from animal experiments to support this concept. However, to the best of our knowledge, our studies provide the first evidence for the importance of this concept in man, namely the negative response to TL in subject W. Y. and the positive followed by a negative response to the eight essential amino acids (EAA #3) in subject V. L. Whether these negative responses would have persisted is not known, nor can any conclusive explanation be offered for their occurrence since both subjects had shown favorable responses to the same or other amino acid supplements at other times. Both of these negative responses were observed late in the experiment when the subjects were approaching zero balance on the basal diet. Whether this is of significance is not known. Also, it is quite possible that these negative effects would not have been observed if the

TABLE III

Urinary Excretion of Arginine, Lysine, and Threonine (mg per 24 hr)

Diet	Amino acid supp.	Subject										
		W. M.			V. L.			R. B.			W. Y.	
		Arg.	Lys.	Threo.	Arg.	Lys.	Threo.	Arg.	Lys.	Threo.	Lys.	Threo.
Normal	—	25	50	46	30	172	46	38	61	55	41	47
Rice	—	19	26	28	19	57	26				30	32
"	TL	22	31	35	22	70	31	19	33	33	25	36
"	TLM	21	33	38	22	69	38	18	32	32		
"	—	20	28	34	22	60	33				26	35
"	NEAA	23	29	38				20	29	29		
"	EAA				21	87	37	19	33	31	32	38
"	—							18	33	29		
"	TLH										33	40
"	—							16	28	31	27	33
Normal	—	34	49	59	40	107	57	23	52	57	37	47

Normal = 85 g protein hospital diet at same calorie level as the rice diets.

The various diets and supplements are listed in the sequence used for W. M. and V. L., but not for the other subjects. This sequence can be determined from Figures 4 and 5.

Each of the values given is the average of three to eight 24-hr urine specimens. Fractions were rounded to the nearest whole number.

diet had provided more variety in protein since the supplementary effect, even of vegetable proteins, is well known.

Most, if not all, of the data obtained in our experiments can be reconciled and explained if the following facts and assumptions are accepted. It is known that most adults can eventually attain N balance on rice-fruit diets supplying 20–25 g protein daily, although several months may be required before balance is achieved.[17–19] In shorter term balance experiments, the findings of Bricker and associates[23] and Hegsted *et al.*[24] indicate that the minimum protein requirement for N balance with mixed all-vegetable protein diets is equivalent to about 2.9 g N per m^2 of body surface. According to this yardstick our subjects would require 5.07 to 5.5 g N daily which in each subject is somewhat above the N supplied by the unsupplemented rice-fruit diets used. When mixed foods were used[23] or when a portion of the vegetable protein was replaced by animal protein[24], nitrogen required to maintain balance was lower, about 2.4 g N per m^2 of body surface.[24] According to this yardstick, our subjects would require 4.2 to 4.56 g N daily. Our rice diets supplemented with TL exceeded these figures in all but one subject (V. L.), and all subjects receiving EAA or NEAA substantially exceeded these minimum figures.

TABLE IV

Amino Acid Requirements of Man Versus Rice-Fruit Diets

Amino acid	350 g rice diet* g	250 g rice diet* g	Rose's[14]	
			Mini. g	Safe g
Lysine	1.12	0.90	0.80	1.60
Threonine	1.27	1.00	0.50	1.00
Methionine (+ Cystine)	1.28	0.98	1.10	2.20
Tryptophan	0.42	0.34	0.25	0.50
Phenylalanine (+ Tyrosine)	3.30	2.61	1.10	2.20
Leucine	2.67	2.11	1.10	2.20
Isoleucine	1.62	1.26	0.70	1.40
Valine	1.96	1.53	0.80	1.60

* These calculations were made from standard literature values[25] for rice and for the remainder of the diet N, amino acid composition similar to vegetable leaf proteins is assumed.[26]

Accordingly it is not surprising that our data indicate a mixture of effects due simply to additional nitrogen and effects probably attributable to improved protein efficiency. It seems clear that a primary deficiency in our diets was a need for more nitrogen, essential or non-essential. The fact that a mixture of non-essential amino acids produced nitrogen retention or a shift in nitrogen balance approximately equal to that produced by a mixture of the eight essential amino acids with equivalent nitrogen would support this view. Further support might be found in the small (statistically not significant) shifts resulting from the very small nitrogen contributions from NEAA #9 and T alone. Thus the positive effects observed with the TL, TLM, and TLH mixtures are probably in part due simply to the nitrogen they supply. L alone, and perhaps methionine, seem to exert a specific effect in some subjects over and above their contribution of nitrogen. The data do not offer any support for a specific effect of T, and, clearly, the human adult is unlike the growing rat where both L and T are necessary to improve rice-protein utilization and where non-essential nitrogen has no beneficial effect. It is entirely possible that T may have interfered with a full L response when TL mixtures were used.

This interpretation as to the "specific" effects of L, and perhaps M, gains some support from a comparison of the amounts of these amino acids calculated to be present in the rice-fruit diets versus Rose's data[14] on amino acid requirements as shown in Table IV. If the figures listed for the rice-fruit diets are reduced by a factor (perhaps 10 to 15 per cent) to allow for digestibility, it is apparent that the diets were mildly deficient or borderline in M and L but equal or exceed "minimum" in other amino acids. Further, it should be recalled that Rose's "minimum" actually represents the highest amount needed by any of his subjects to achieve N balance and that there is a range of individual minimum requirements below (and possibly above) this figure. Also, it is possible that the availability of different amino acids in rice may vary, and this in turn might vary in different subjects. Thus it seems entirely logical that some of our subjects

would respond to L or M while others would not.

The negative effect of TL and of EAA #3 in two subjects might be explained on the following basis. It is clear that some sort of an adjustment to these diets occurred with time. In the first 4 to 30 days on the rice-fruit diets the urinary nitrogen alone exceeded the total diet N intake. This changed gradually to a point where in most subjects balance or near balance was achieved on the supplemented diet. The mechanism(s) of this adjustment is not known. However, it is obvious that a situation results where the protein and amino acids are more efficiently utilized, or metabolic processes come into play which change the amount of a particular amino acid needed. Thus it is possible to visualize that the suddenly added amino acids might upset these "adaptive" changes and result, temporarily at least, in less efficient protein utilization. Or, according to the concept of amino acid imbalance, addition of an amino acid(s) could result in an unphysiologic amino acid mixture being presented to the cells so that "surplus" amino acids interfere or compete with utilization of other needed amino acids with less efficient utilization being the result. The unfavorable effect of the TL mixture might have been due to precipitating a methionine deficiency.

Studies on the arginine, lysine, and threonine concentration in serum proteins were prompted by the report of Albanese[27] which indicated a progressive increase in the concentration of arginine in one or more of the plasma proteins of infants consuming a lysine-poor diet (wheat gluten). This change could be reversed by lysine supplementation. Since our diets were (presumably) lysine-poor, and relatively rich in arginine, it seemed possible that changes similar to those reported by Albanese might be found. However, no changes were observed under our conditions.

SUMMARY AND CONCLUSIONS

The nitrogen balance technic was used in five normal young adult males to evaluate certain amino acids as supplements in rice diets. Rice (250 or 350 g), fat (100 g), fruit, and sugar were used to prepare constant diets providing 26 to 31.7 g protein and 2,800 to 3,500 calories (39 to 50 cal/kg body wt).

Lysine alone induced a positive shift in N balance in one subject. Threonine alone was ineffective. Lysine and threonine together had a highly significant positive effect in one subject, questionably positive effects in two others, no effect in a fourth, and a highly significant negative effect on nitrogen balance in a fifth subject. The addition of methionine resulted in a positive shift in N balance in the subject who failed to respond to threonine and lysine alone. In another test the threonine, lysine, and methionine mixture did not improve the response beyond that produced by threonine and lysine alone. A mixture of threonine, lysine, and histidine produced a positive response in one trial. Mixtures of the eight essential amino acids resulted in positive shifts in two trials. In a third trial the response was significantly negative. A mixture of non-essential amino acids produced positive effects approximately equal to that with the eight essential amino acids.

These results are interpreted as indicating that a primary deficiency in these diets is that of available nitrogen, essential or non-essential. The positive effects of the amino acid supplements are interpreted as being due in part to the nitrogen supplied. Lysine, and perhaps methionine, seemed to exert a "specific" effect in improving protein utilization over and above their nitrogen contribution in some, but not all subjects. No evidence for a similar effect of threonine or other amino acids was obtained.

The highly significant negative response to lysine plus threonine in one subject and to a mixture of the eight essential amino acids in another is interpreted as providing evidence for the importance of amino acid balance in man.

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Vitamin B_{12} Absorption in Pregnancy and in the Newborn

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INCREASING interest is being shown in the role of vitamin B_{12} in pregnancy and in its transfer from mother to fetus. In a previous communication,[1] it was reported that a considerable quantity of radioactivity is transferred to the fetus when pregnant rats are injected with vitamin B_{12} labeled with $Cobalt^{60}$. Later it was demonstrated that serum vitamin B_{12} levels in the fetus at the time of delivery, measured from the umbilical cord blood, are invariably higher than those of the mother obtained at the same time.[2] This apparently "parasitic" action of the fetus in relation to its mother's vitamin B_{12} content has led us to study whether the pregnant woman, or rat, possesses a mechanism of compensation against excessive depletion of her vitamin B_{12} stores. The results of such a study, and some additional incidental findings regarding methods of studying this problem, are given in this report.

DETERMINATION OF THE ABSORPTION OF VITAMIN B_{12} BY PREGNANT AND NON-PREGNANT WOMEN

In view of a general, and understandable hesitancy on the part of obstetricians to ask mothers to allow their unborn or newborn infants to be subjected to the effects of radioactivity, however safe this may be, the following method of studying absorption was used:

Two groups of women, one pregnant and one non-pregnant group, were subdivided into three subgroups. The non-pregnant group consisted of women of childbearing age and of comparable background to the pregnant group. All women in subgroup A were given an oral dose of 1,000 μg of vitamin B_{12} while subgroup B and C received 500 μg and 250 μg respectively. Serum vitamin B_{12} levels were obtained on all subjects prior to vitamin B_{12} administration and one and one-half and three hours after the administration.

The resultant serum vitamin B_{12} levels are shown in Table I. An increase in serum vitamin B_{12} level of more than 160 μg is taken as a positive response, since this order of magnitude is beyond the error of our routine assay for this vitamin.

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ABSORPTION OF VITAMIN B_{12} IN PREGNANT AND NON-PREGNANT RATS

Determination of Serum Level: In two separate studies, conducted three months apart, 26 adult female rats (three to four months old) were used. In each study the animals were bled by cardiac puncture, and 1.5 ml of blood was obtained for vitamin B_{12} assay according to the procedure described by Okuda[2,3]. The rats were randomly divided into two groups, A and B. Animals in group B were mated with adult male rats, while animals in group A served as controls. In both studies all mated animals became pregnant within four weeks. Shortly (one or two days) prior to delivery, rats in both groups A and B were again bled for B_{12} assay. The results of this study are given in Table II.

Determination of the Absorption of Vitamin B_{12} by Pregnant and Non-Pregnant Rats: The absorption of vitamin B_{12} by pregnant and non-pregnant rats was measured by feeding a measured amount (50 $\mu\mu$g) of radioactive vitamin B_{12} orally with a specific activity of 1,000 microcuries per mg. Two hours after feeding, the animals were injected with 50 $\mu\mu$g of unlabeled vitamin B_{12}. All animals, housed individually in separate cages, were given a basal casein diet.[4] Urine and feces were collected separately for eight days at

two-day intervals. The details for the determination of radioactivity in the excreta are described in our previous communications.[5,6] The results of two studies performed at least three months apart are given in Table III. Half of the animals in each of the two study groups were mated and became pregnant. About ten days before delivery both pregnant and control rats were given 50 mmcg of vitamin B_{12} by mouth. The radioactivity in the urine and feces was determined by scintillation counting. The differences between the radioactivity of orally administered vitamin B_{12} and the fecal radioactivity is taken as a measure of the absorbed vitamin. The radioactivity in the fetus was also determined after digesting the tissues with 30 per cent KOH.

Determination of Radioactivity in Maternal Liver and Kidney and of the Fetus following Subcutaneous Administration of Radioactive Vitamin B_{12}: Twenty-four female adult rats (three to four months old) were used in two separate studies conducted four months apart. Half of the animals in each study were mated with adult males and the other half served as controls. Two or three days before delivery both pregnant and non-pregnant animals were injected subcutaneously with 10 $\mu\mu$g of

TABLE I

Response of Pregnant and Non-pregnant Women to Oral Tolerance Test for Vitamin B_{12}

Dosage in μg	Pregnant		Non-pregnant	
	Av. change in μg	Response, %	Av. change in μg	Response, %
250	15.5 (10)*	0	47 (10)	0
500	198.3 (13)	41.5	128 (12)	16.6
1,000	262.8 (9)	88.8	157.5 (7)	28.5

* Numbers in parenthesis denote the number of subjects used.

TABLE II

Plasma Vitamin B_{12} Levels of Pregnant and Control Rats

Study	Group	No. of rats	Serum B_{12} content in $\mu\mu g/ml \pm$ S.E.M.*		
			Before mating	Before delivery	6 weeks later
I	A	6 (control)	1.2 ± 0.06	—	1.1 ± 0.1
	B	8 (mated)	1.2 ± 0.12	0.66 ± 0.04	—
II	A	6 (control)	1.15 ± 0.09	—	1.1 ± 0.08
	B	6 (mated)	1.2 ± 0.14	0.6 ± 0.02	—

* S.E.M. Standard error of the mean.

TABLE III

Absorption of Orally Administered Vitamin B_{12} to Pregnant and Non-pregnant Rats

Study	No. of rats	Vitamin B_{12} activity in*			
		Urine	Feces	Absorbed B_{12}	B_{12} in fetus
I	8 (pregnant)	0.6 ± 0.05	10 ± 1.2	40	24 ± 3.6
	8 (control)	0.4 ± 0.12	29 ± 3.6	21	—
II	6 (pregnant)	0.5 ± 0.10	9.6 ± 0.8	40.4	26 ± 2.8
	6 (control)	0.35 ± 0.15	31 ± 2.9	19	—

* Expressed in $\mu\mu$g of vitamin B_{12}.

radioactive vitamin B_{12} and were sacrificed four days later. The livers and kidneys of the mothers and of the non-pregnant rats were assayed for their radioactivity contents, as were the offspring in their entirety. The results are shown in Table IV.

RESULTS

Pregnant women who were fed a dose of 1,000 μg of vitamin B_{12} showed a statistically significant increase in absorption of the vitamin as compared to non-pregnant women. An increase in serum vitamin B_{12} of 160 $\mu\mu$g per ml or more was found in eight out of nine pregnant women, as compared with only two out of seven non-pregnant women. When the test dose was reduced to 500 μg the difference was not statistically significant, although it is suggestive of the greater absorption by the pregnant subjects. When the dosage was reduced further to 250 μg no significant increase in the serum level was observed in either group. When the results of the two higher dosages are taken together, the data again show that in pregnant women there is statistically significant greater absorption of vitamin B_{12}.*

This phenomenon was supported by results of experiments with rats. Thus, data tabulated in Table II clearly indicate that the vitamin B_{12} serum level decreased to almost one-half of its original value in the course of pregnancy. This result is clearly shown by comparing the serum vitamin B_{12} level of the rats with either the mean value of the same rats before mating or with the mean value of the non-pregnant controls. The serum vitamin B_{12} level of the control animals would suggest that the relatively lower levels during pregnancy are not the result of the process of bleeding.

Results in Tables III and IV indicate that the absorption of orally administered radioactive vitamin B_{12} is greater in the pregnant than in the non-pregnant rats. The increase in the absorption is approximately twofold (from approximately 20 $\mu\mu$g to 40 $\mu\mu$g). It is interesting to note also that 60 per cent or more of the absorbed vitamin was concentrated in the fetus. The extraordinary ability of the fetus to draw vitamin B_{12} is again demonstrated in the experiment in which both pregnant and control rats were given 10 $\mu\mu$g of Co^{60}-labeled B_{12} by the subcutaneous route. About 60 per cent of the injected vitamin B_{12} was concentrated in the fetus. More surprising, however, is the fact that the target organs of the pregnant animals contained much less radioactivity than those of the controls. These results, taken as a whole, indicate clearly that in pregnancy the absorbed vitamin B_{12} is concentrated in the fetus.

TABLE IV

Comparison of the Fate of Vitamin B_{12} Injected into Pregnant and Non-pregnant Rats

Study	No. of rats	Vitamin B_{12} content expressed as $\mu\mu$g in			
		Liver	Kidneys	Fetus	$\mu\mu$g/fetus
A	6 (pregnant)	0.32 ± 0.06	0.17 ± 0.04	6.2 ± 1.0	0.6 ± 0.2
	6 (control)	1.3 ± 0.12	0.8 ± 0.10	—	—
B	6 (pregnant)	0.75 ± 0.17	0.28 ± 0.09	5.96 ± 0.8	0.46 ± 0.04
	6 (control)	1.50 ± 0.08	0.86 ± 0.10	—	—

Possible Interrelationship between Thyroid Activity and Vitamin B_{12} Metabolism: From what has been stated before, the fetal capacity for obtaining vitamin B_{12} from the available maternal supply is remarkable. It has been previously reported by the authors[2] that in spite of very low maternal serum vitamin B_{12} levels, the fetus could still show adequate or high serum levels. At that time allusion was made to the fact that the fetus of Case V,[2] in which neither the mother nor the fetus showed an appreciable serum level of vitamin B_{12}, had been admitted to the Pediatric Service of the Johns Hopkins Hospital with a classic picture of cretinism. An initial speculation as to a possible relationship between a depleted fetal vitamin B_{12} level and hypothryroid-

* $X^2 = 4.33$; significant $X^2 = 3.8$ (X^2 = chi sq)

ism was made at that time. Since then, a second case of athyroid cretinism has been admitted to the Johns Hopkins Hospital, in which the same fetal phenomenon was observed.

As a result of the findings in these cretins, studies were carried out in the Harriet Lane Home for Children which show that the administration of thyroid extract to cretins in infancy will rapidly return the vitamin B_{12} levels to normal.

At birth the second infant had no appreciable amount of vitamin B_{12} in the serum, while none was detected in the mother's blood at delivery. Six weeks postpartum, the mother's serum vitamin B_{12} level was noticed after initiation of thyroid therapy. Unfortunately there was no maternal vitamin B_{12} serum level available in this case.

Since in our previous report[2] the occurrence of very low maternal serum vitamin B_{12} levels is reported in the presence of normal or high fetal serum levels, and since the low fetal serum vitamin B_{12} levels were only obtained in those cases which clinically showed evidence of cretinism, we suggest that the fetal serum vitamin B_{12} level, rather than the maternal, is a significant finding in cretinism. The results of these studies are reported in Table V.

Because the incidence of cretinism is low, and because there is an even smaller likelihood of obtaining maternal and fetal serum vitamin B_{12} levels at the time of delivery of cretins except by the routine assay of these levels on thousands of cases, we have considered it worthwhile to report our findings on the aforementioned two cases in the hope of stimulating similar studies in other medical centers.

TABLE V

Thyroid Activity and Vitamin B_{12} Serum Level in Cretinism

	Date	Age	P.B.I.*	Clinical picture	Thyroid therapy	B_{12} serum level†
Patient D. W.	8/12/55	Birth	—	—	0	0
	10/7/55	7 weeks	0.6	Severe hypothyroid	Started on 1/4 g/day	0
	11/22/55	3 1/2 months	4.7	Euthyroid	3/4 g/day	157
	12/7/55	4 months	4.9	Euthyroid	3/4 g/day	222
	1/6/56	5 months	—	Euthyroid	3/4 g/day	325
Patient T. F.	3/28/56	7 weeks	2.0	Moderately hypothyroid	Started on 1/2 g daily	<50
	4/11/56	9 weeks	3.7	Slightly hypothyroid	3/4 g/day	303
	6/16/56	4 months	6.2	Euthyroid	1 g/day	—

* Protein-Bound Iodine.

† Expressed in $\mu\mu$g.

tamin B_{12} level had returned to normal without thyroid or vitamin B_{12} therapy. The infant's serum vitamin B_{12} level did not return to normal levels until after thyroid therapy had been initiated, the rise was rapid thereafter.

At the time of the initial diagnosis of cretinism (seven weeks after birth) the infant had a protein-bound iodine of 0.6 mg per 100 ml, no uptake of radio-iodine over the lower neck region, and a bone age revealing retardation to a seven months' intrauterine fetal level with epiphyseal dysgenesis of the talus of the foot. This latter finding indicates that this infant had been hypothyroid *in utero*. The second infant's radio-iodine uptake at seven weeks was also zero. Again the rapid rise in the serum

SUMMARY AND CONCLUSIONS

Absorption of orally administered vitamin B_{12} is significantly increased by pregnancy in the human and in the rat. As yet, pregnancy is the only known method of increasing vitamin B_{12} absorption in the adult.

In spite of increased vitamin B_{12} absorption,

the serum vitamin B_{12} level and the vitamin B_{12} content of the liver and kidney of pregnant rats actually show a decrease, presumably due to the demands of the fetus which seems to be the main beneficiary of the increased vitamin B_{12} absorption rate in pregnancy.

Oral tolerance tests can be used as a method of proving increased vitamin B_{12} absorption, provided the administered dose is large enough. The critical test dose in the experiment reported was 1,000 μg. This method of study obviates the use of radioactive materials in the pregnant state.

There is an, as yet, imperfectly understood relationship between thyroid function and vitamin B_{12} absorption in the earlier stages of life. It is suggested that abnormally low vitamin B_{12} serum levels may be found in the blood of newborns with cretinism. Administration of thyroid to newborn cretins rapidly raises the serum vitamin B_{12} to normal levels.

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Nutrition and Behavior

AN EPILOGUE

By JOSEF BROŽEK, PH.D.*

FOR THE MOST part the authors of the individual contributions to the recent Symposium on Nutrition and Behavior in this Journal† presented the results of specific, original investigations. Neither the available time nor the framework of the symposium were conducive to the consideration of any but the most directly relevant literature. While no systematic analysis and exhaustive bibliography of the literature in this highly fractionated field can be attempted here, a brief survey of current trends and selected recent publications may usefully supplement the symposium.

BOOKS AND REVIEWS

The only available book-length treatment of the psychology of diet and nutrition, by Selling and Ferraro,[1] is twelve years old. In view of the premature death of the senior author, the volume is not likely to be published in a second edition. While unquestionably it has been a significant, pioneering contribution, it was directed principally to those who might *use* the information on better feeding of people —be they clinical dietitians, industrial or institutional meal-planners, or housewives. It makes no scientific pretenses and lacks the rudimentary paraphenalia of a learned biologic treatise such as tables, graphs, and references. The symposium currently published does not fill the existing vacuum in any but a partial and temporary manner.

The best general bibliography of studies in the field of psychodietetics, supplementing Fritz's work[2] with a rich harvest of experimental studies, is contained in the *Manual for the Study of Food Habits*,[3] now also 12 years old. In the text of the *Manual* Part V, devoted to experimental methods, is the most relevant. In Spillane's work[4] on nutritional disorders of the nervous system numerous references are appended to single chapters. Literature on semistarvation is interwoven with the results of the experimental study carried out at the University of Minnesota.[5] In the second volume, the section on *Psychology* considers some general, principally methodologic problems, behavior and complaints under "natural" and experimental conditions, intellective functions, and personality. Several case studies are presented in detail. Special senses and neuromuscular functions are discussed in the first volume.

The field of "psychodietetics," with special reference to experimental studies on man, has been surveyed on the occasion of the Third International Congress on Nutrition.[6] A brief review of the influence of dietary deficiencies on psychologic functioning was prepared by Bakwin.[7] Regretfully, we have had no opportunity to consult the report presented recently before the German Nutritional Society.[8]

CLINICAL AND FIELD STUDIES

In 1943 Sebrell[9] expressed the opinion that in pellagra the mental changes constitute one of the most interesting phases of the disease: "Here for the first time is a major psychosis for which we have a specific therapeutic agent and we are able to make a reasonable guess that the underlying trouble is an altered brain metabo-

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† Nutrition and Behavior, AM. J. CLIN. NUTRITION 5: 103–211, 1957.

This survey was prepared in the framework of investigations on *Nutrition and Performance Capacity*, (Contract DA44-109-qm-1526), jointly supported by the Quartermaster General and the Surgeon General of the Department of the Army. The comments contained in this report reflect the views of the author.

lism." Sebrell felt that perhaps Goldberger's greatest contribution to medicine may turn out to be not the discovery that pellagra is a dietary deficiency but the first recognition of a specific treatment for a psychosis. The role of niacin in the etiology and therapy of psychiatric disorders, with special reference to pellagra but not neglecting other disorders, was reviewed in detail by Gregory.[10] An overall review of nutrition and metabolism in relation to neurology and psychiatry was presented by Campbell.[11]

One of the dramatic recent developments in therapy has been the hope for a control of one form of mental deficiency, phenylpyruvic oligophrenia,[12] through dietary means. Here we deal not with a dietary deficiency but with a faulty metabolism. The amino acid phenylalanine is not metabolized normally. It accumulates in body fluids, including the cerebrospinal fluid, and is converted into phenylpyruvic acid which the patients are also unable to oxidize. By maintaining patients with phenylpyruvic oligophrenia on diets low in phenylalanine during the first years of life great improvement in mental functioning has been obtained.[13–15]

Possible therapeutic effects of feeding glutamic acid continue to be studied in patients with psychiatric disorders. The work of Himwich *et al.*[16] stands out as a good example of a multidisciplinary approach including, as it does, the consideration of the psychologic, physiologic and biochemical aspects of the problem. Unfortunately, the patient population studied was highly heterogeneous so that the groups, characterized by specific syndromes, became too small to allow valid generalizations.

Harrell, Woodyard, and Gates[17] reported the results of a large-scale investigation of the effects of mothers' diets on the intelligence of the offspring. In this study the diet of pregnant and lactating women was supplemented with certain vitamins. During follow-up, the Terman-Merrill version of the Binet test of intelligence (Form L) was given to 811 three-year-olds in rural Kentucky (white), and to 518 three-year-olds and 370 four-year-olds in Virginia (predominately Negro). In Kentucky the mean I.Q. for the total group was 107.6 and there was no significant difference between experimental groups. In Virginia the average I.Q. values were 103.4 (children of mothers receiving a polynutrient supplement), 101.9 (2 mg thiamine), 100.9 (200 mg ascorbic acid), and 98.4 (placebos). The difference of 3.7 points between supplemented and placebo group was statistically significant but no relative superiority of any of the three types of supplements could be demonstrated statistically.

Hyperirritability, combined with apathy, and anorexia were repeatedly noted among the clinical characteristics of severe protein malnutrition of children (kwashiorkor, sindrome pluricarencial de la infancia).[18] The psychologic manifestations of the malnourished child were examined specifically by a group of investigators at Hospital Infantil, Mexico City.[19] The behavior manifestations differ at different levels of malnutrition. The authors differentiate three degrees, characterized by weights of 20 to 25, 25 to 40, and more than 40 per cent below the standard weight. Direct observation, interviews of the mothers, and Gesell's technic of appraising the level of behavioral development were used. Only a preliminary report, lacking details, is available at the time of this writing.

At Kampala (Uganda) the psychologic changes accompanying kwashiorkor are being studied by Geber and Dean.[20] As a background, the psychomotor development of "normal" African children, aged 6 months to 6 years was charted.[21] For 25 children who were acutely ill with kwashiorkor the behavior at three stages of recovery was described in terms of qualitative observations and results obtained on the Gesell tests. The quantitative estimates, not presented in a tabular form, were based on the performance in individual tests making up the scale and were evaluated in reference to locomotion, manual ability, adaptive behavior, language, and personal-social behavior.

So far we have considered the psychologic effects of nutritional alterations. We dealt with "somatopsychology." On the psychosomatic side, hypnosis has received increased at-

tention in recent years as to both theoretic analysis of hypnotic phenomena and uses in therapy.[22] Applications of hypnosis to a variety of diseases associated with nutritional aberrations were described by Fogelman and Crasilneck.[23] These applications of hypnosis were reported to be effective in increasing total caloric intake, allaying specific food restrictions, and dulling pain and symptoms of gastrointestinal disorders which resulted in loss of appetite.

The significance of cultural factors (and, on occasion, of the competence of cultural anthropologists) in nutritional studies was brought out by Wallin.[24] Food habits are thoroughly immersed in culture and affect food intake as importantly as the soil, climate, and the stage of economic and agricultural development. Wallin noted that ethnographic accounts may identify "natural experiments" in nutrition and he uses kwashiorkor as a type of malnutrition in which the consideration of cultural factors appears to be significant. As to culturally conditioned "natural experiments," Žarković *et al.*[25] contrasted two groups of the same national (Serbo-Croatian) origin but differing in religion. The Orthodox (Serbs) tended to have a higher dietary fat intake (and higher serum cholesterol level) than the Moslems. The study was a part of a broader project of medico-ecological investigations of the village population in and near Trnovo in Bosnia-Hercegovina. Interesting information on the interrelation between the culture of a population and introduction of new foods was presented by Chen and Tung[26, 27] in their description of the rice enrichment project in Taiwan.

Age is an important variable in considering either the physiologic or psychologic aspects of feeding. While in the past most of the attention was devoted to the feeding of children, the growing interest in gerontology and geriatrics is reflected in concern with the emotional aspects of feeding the aged.[28]

NUTRITION AND HUMAN PERFORMANCE—METHODOLOGY

After all is said and done about nutritional adequacy and status, it is the real-life performance that "counts"—in schools, in mines, in industry, in agriculture, on the battle field. The skill with which the pilot handles his plane during combat, the endurance of foot soldiers during a long march, a marine's speed of motions and strength in hand-to-hand combat, the accuracy with which a submarine follows the movements of an enemy vessel on the basis of data taken from the radar scope—these are the final and irrevocable criteria of "fitness." Why, then, has not more attention been paid to performance in reference to nutritional status?

There are several reasons. Experimentation, using the *actual* performance is, as a rule, not feasible and in most situations information on the quantifiable aspects of performance is not readily obtainable. It is only under rare conditions, such as rigorously controlled rationing, that caloric intake may be examined in reference to industrial output.[29] Under normal conditions, controlled studies on industrial efficiency as affected by food intake can be carried out only when some food is added, *e.g.*, a snack during midmorning and midafternoon rest periods.[30] No experimental work on quantitative or qualitative deprivation in industry seems feasible.

The fact that performance represents a product of capacity and motivation should not be forgotten. This places heavy demands on the experimenter who must be concerned not only with the control of the dietary factors but also with the "human" atmosphere in which he carries out his work and which may be altered as a result of his activity beyond any direct impact of nutrition.

In the laboratory, the experimenter can use either simplified performance tests (miniature work situations)[31] or more abstract tests of motor and sensory functions.[32] In fundamental studies in which there is a reason to suspect alterations in nervous function, intellective performance should also be included, even though the factual information obtained so far indicates a surprising stability of measured intelligence under nutritional stresses. The exploration of personality changes is indicated by the important role of motivation in performance.

The overwhelming majority of psychomet-

ric instruments were designed for a single administration whereas in nutritional research we are concerned with examining potential changes in "nutritional status" over time. This requires repeated testing and gives rise to several types of difficulties.

In some areas, adequate instruments have not been available. Thus a repeatable battery of six tests of relatively "pure" components of intellective ability, with a sufficient number of alternative forms, was assembled for purposes of nutritional research.[33] This battery of tests took about 30 minutes to administer at a single testing session. About 20 practice trials were needed, at intervals of two to three days, to bring the test scores to a plateau. Thereafter, performance could be maintained at this plateau, in the absence of a stress, by administering the battery every three to four weeks.

Limited information, crucial to the planning of experimental investigations, has been available on the number and frequency of testing trials needed in order to attain a stable practice plateau in psychomotor tests. This problem was examined systematically,[34] together with the consistency of repeated measurements, intercorrelations between the test scores at the outset and again at or near the practice plateau, and the sensitivity of different functions to experimental, including nutritional stresses in man.

EXPERIMENTAL STUDIES ON HUMAN NUTRITION

Experimental studies on the impact of variations in man's diet are difficult, partly because of the time involved, unless one is dealing with variables, such as beverages stimulating the central nervous system, the effects of which manifest themselves rapidly.

In this context, a small monograph should be mentioned, devoted to the pharmacologic, physiologic and psychologic effects, and dietary and medical appraisal of tea.[35] The general psychologic and psychiatric aspects are discussed by Lawton[35] and Jenkins.[36] An experimental study of the psychophysiologic effects was reported by Stanley and Schlosberg.[37] Twenty-two housewives served as subjects. Out of a fairly large battery of tests the most marked and most consistent effect was improvement of simple auditory reaction time. Complex reaction time to visual stimuli showed an effect in the same direction but smaller in magnitude. The "positive" results were noted immediately following the ingestion of tea as well as during tests made 30 minutes later. While the increased "alertness" in the delayed tests may be regarded as a pharmacologic effect, the gain on tests immediately following the ingestion of tea can hardly be ascribed to the pharmacologic action of the active ingredients of tea, principally caffeine. The immediate effects are not clearly understood at present. The experimenters used a pause without tea as their control. It appears that use of hot water would have provided a better reference point and would better serve the purpose of separating the pharmacologic from the non-pharmacologic effects.

Typically, nutritional research extends over periods of not minutes or hours but weeks and months. This represents a heavy investment both of time, on the part of the subjects and the research staff, as well as laboratory facilities and money. A rigorous dietary control may involve far-reaching restrictions on the freedom of movement of the subjects and severe dietary restrictions may have a profound impact on personality.[38]

These considerations restrict the feasibilty of experimental work on nutritional deficiencies, especially those severe enough to affect nervous function and behavior, to special situations, with adult volunteers serving as subjects. In the Laboratory of Physiological Hygiene the subjects were drawn from the ranks of personnel of the Armed Forces, conscientious objectors and, in shorter exploratory studies, from among medical students.

Psychologic changes in acute starvation, combined with hard physical work,[39] were examined in a series of investigations on physiologic stresses interposed in the course of a study on thiamine requirements. While tests of intellective functions showed little or no impairment after four days of starvation, statistically highly significant deterioration occurred in tests of speed and of eye-hand coordination. There was a large increment on the psychoneurotic scales of the Minnesota

Multiphasic Personality Inventory. Tiredness, feelings of muscular weakness (with no counterpart in a decreased measurement of strength), and soreness of muscles dominated the subjective symptoms.

Information provided by this study throws additional light on alterations in man's performance capacity under physiologic stress of nutritional origin. The study, carried out initially in a different context, provides valuable background for the "applied" research on the reduction of deterioration in fitness resulting from feeding emergency (survival) rations.

With the emergency rations providing 1,000 calories per day, it was possible to maintain normal young men for 24 days without disabling alterations in performance capacity or morale.[40] The initial nutritional status of the subjects was good and they were in a good state of physical training. Throughout the experiment they were engaged in a moderate amount of physical exertion in a moderate climate. They had free access to water, with adequate salt intake and vitamin supplements. Measurements of visual functions and hearing revealed no deterioration. The alterations in psycho-motor functions were surprisingly small. Statistically significant changes were limited to the speed of single, large ballistic leg movements (upward thrust) and to fairly gross movements of the arms and the body involved in the "travel" from switch to switch in the motion analysis test, constructed and operated by Prof. K. U. Smith and Dr. S. Harris of the University of Wisconsin. In personality questionnaires the changes were small.

Carefully managed metabolic experiments on niacin deficiency were reported by Goldsmith and her co-workers.[40a] The subjects were characterized as having been essentially free of organic disease and having "some form of psychoneurosis."[40b] As would be expected, depression and apathy, in the absence of demonstrable neurologic changes, were noted frequently as part of the deficiency syndrome, but no quantification of this response was attempted.

ANIMAL BEHAVIOR—METHODS

Animal behavior has several parameters that are of interest in reference to nutritional research. In the Symposium on Nutrition and Behavior* the authors of experimental papers considered such varied aspects of animal behavior as differentiation between two tones by lifting the foreleg at the sound of a tone previously associated with a faradic shock; activation of a heat lamp in a cold environment by albino rats deprived of pantothenic acid and later submitted to starvation; and food consumption.

Experimental investigations on bodily needs[41] have gained substantially from using quantitative methods for the study of general activity, such as running, for the amount of food eaten or of water drunk, and for the time characteristics of food ingestion.

Anliker and Mayer[42] described in some detail the "operant conditioning" technic for studying the temporal feeding patterns of mice, making possible what the authors termed a fine-grained analysis of feeding behavior. The animal releases small pellets of food by depressing a lever. The activation of the lever is recorded and the cumulative frequency curve provides a permanent record of rate of feeding. The general aspects of the use of a free operant in the analysis of behavior were presented by Ferster.[43] It was noted that this method of research has a wide applicability in experiments in which the frequency of behavior is the main dependent variable.

In the field of pharmacodynamics, which has much in common with experimental research on nutrition, a whole symposium (under the chairmanship of Dews and Skinner[44]) was devoted to the description and evaluation of technics for the study of behavioral effects of drugs. The methods that were utilized included such approaches as quantification of spontaneous behavior patterns—sociability, contentment, excitement, hostility—in cats, superimposition of conditioned emotional (fear) responses on lever pressing (as "non-emotional behavior") in rats, pecking rates in pigeons, spaced responding in albino rats and discrim-

* Am. J. Clin. Nutrition 5: 103–211, 1957.

inatory responses to a simple, two-component pattern of visual stimuli.

These animal studies, frequently utilizing the pressing of a lever or pecking at a panel as the instrumental response, were concerned principally with consumatory behavior, rather than with "performance." Elsewhere[45] we have stressed that the technics for the study of such aspects of performance capacity as learning (running dry and water mazes, acquisition and maintenance of conditioned responses) and problem solving, and, in particular, of endurance, have received less attention on the part of the nutritionists than they deserve.

In the symposium for the study of behavioral effects of drugs, Miller[46] stressed the value of using a variety of measures in analyzing the effects of drugs on motivation. The diversity of technics should reduce arriving at misleading generalizations on the basis of effects that may be specific to a particular indicator. One of the technics used in studies carried out by Miller and his associates involves measurement of strength with which the animal pulls against a temporary restraint.

While instrumental responses have the appeal of simple and efficient registration, there is also merit in the standardization of naturalistic observations. In situations which are complex, such as the behavior of monkeys in cages, the application of systematic direct observational methods makes possible an objective appraisal. McDowell *et al.*[47] are concerned with the symptoms of radiation sickness but the principles are applicable also to some nutritional problems. The kinds of behavior, established in the course of a preliminary taxonomic study, that occurred in time-sample observations of the caged laboratory monkeys were described verbally by the observer and recorded on a tape. Use of motion pictures would provide a permanent, "public" record available for subsequent analysis, while recording the observed kinds of behavior directly on the punch cards would eliminate the transcription and analysis of tape recordings.

DIET AND ANIMAL BEHAVIOR

In his comprehensive review of the literature on sound-precipitated convulsions, Bevan[48] considered the effects of dietary factors upon susceptibility to seizures. Among the nutrients that were studied were vitamins of the B-complex, sugars (glucose, lactose, dextrose), lysine, glutamic acid, and magnesium.

The area of diet selection continues to be cultivated with profit. Harriman[49] has shown that previously vitamin A-depleted rats ingested significantly larger amounts of the provitamin A-bearing (alfalfa) meal than the control group when it was made available to them. The same author[50] reported that rats, given the opportunity to establish during the control (preoperative) period a strong preference for sugar over salt, maintained the preference subsequent to adrenalectomy and failed to manifest the expected increase in salt intake. In this situation a preoperative fixation of a food preference interferred with the selection of needed factors which would compensate for the altered regulators of the animal's internal environment.

Griffiths[51] investigated the nutrient selections of domestic Norway rats subjected to the stress of treadmill running. Out of 15 substances offered in solution, five were selected in different amounts during the treadmill-running periods. While the biologic significance of the altered pattern of intake is not altogether clear, it was noted that the largest increase took place in the intake of calcium pantothenate, with average amounts of 2.0 and 9.0 ml of the solution ingested prior and during treadmill running.

HUNGER, APPETITE, AND SATIETY

The problems concerning the initiation and the termination of eating are being intensively studied. A conference held under the chairmanship of Hollander[52] and the aegis of the New York Academy of Sciences was devoted to the fundamental analysis and clinical aspects of the mechanisms regulating food intake. The proceedings constitute an up-to-date presentation of current theories—this still being in the plural, with emphasis placed on the role of the digestive tract, glucostatic mechanisms, and multiple factors. The emotional aspects of eating were considered from the point of view of the psychiatrist; cravings

and aversions as well as clinically useful appetite depressants were discussed.

Miller[53] brought out the shortcomings of food consumption as a measure of "hunger" (see also Ref. 46) and stressed the usefulness of other behavioral technics. Thus it was found that rats with hypothalamic lesions on an *ad libitum* feeding schedule ate much more food than did the normal controls and, in due time, became obese. However, it was shown in a series of behavioral tests that they worked *less hard* for food and were *more easily* deterred from eating it, i.e., they reacted to food deprivation with a less intense "hunger."

The mechanism of satiety is justifiably in the center of attention. Stunkard *et al.*[54] found that the administration of glucagon (the pancreatic hyperglycemic glycogenolytic factor), followed by a rise in blood glucose levels and an increased peripheral capillary-venous blood glucose difference, resulted in prompt abolition of gastric hunger contractions, coinciding with decrease in the experience of hunger. The findings are regarded as fully compatible with Mayer's "glucostatic" theory of regulation of food intake. However, there are dissident voices in the chorus.

In a study considered as an experimental test of the glucostatic theory of regulation of hunger, Bernstein and Grossman[55] induced hyperglycemia in normal young adult males by intravenous or intragastric administration of glucose, with control treatments consisting of administration of saline by these routes. Neither the food intake nor "appetite," as evaluated subjectively, was significantly altered by the glucose treatment and the authors concluded that the glucostatic theory is not supported by the results of their study.

Fryer *et al.*[56] using isocaloric reducing diets, found no correlation between the capillary or venous glucose levels or the capillary-venous difference, on one hand, and the satiety value of the diets, on the other hand. On the contrary, the high-protein diet, superior in providing satiety, was associated with the lowest blood glucose levels. These findings are considered as incompatible with the glucostatic theory of appetite regulation.

Mayer[57] surveyed the recent literature on the physiological basis of obesity and leanness, with special reference to the work done by his group.

OBESITY AND WEIGHT REDUCTION

In a psychiatric study on obesity among women, Hecht[58] stressed the inseparability of components of the problem: the meaning to the patient of food, of eating and of the obese state itself. The author feels that it is impossible to understand the nature of obesity or an obese individual's inability to lose appreciable amounts of weight and maintain that reduction, unless one considers the psychologic aspects as primary. While one might be tempted to debate details of the author's psychodynamic interpretation, experience confirms the conclusion that the prognostive importance of the psychologic factors certainly can not be overemphasized.

Stunkard *et al.*[59] described the "night-eating syndrome," a distinctive eating pattern among certain obese patients, with insomnia and morning anorexia. Patients manifesting the syndrome had great difficulty in losing weight and experienced a high incidence of a variety of complications in their endeavors for weight reduction.

The psychologic aspects of obesity, including personality characteristics of the obese[60] and group methods in weight reduction[61] were considered at the Weight Control Colloquium held at Ames, Iowa.[62] The proceedings of the conference should be noted for the efforts of its organizers to transcend departmental lines and to consider the contribution of disciplines concerned with man's behavior (psychology, sociology, education) alongside the more classical partners of the science of nutrition, such as biochemistry and physiology.

Young *et al.*[63] on the basis of experience in a community nutrition clinic, felt that success in weight reduction was related primarily to the emotional stability of the candidates. It was suggested that one of the greatest needs of the practicing physician or outpatient weight-control clinic is for workable methods of evaluating emotional stability of the patients, this being one of the important criteria of suitability for weight reduction.

The relationship between emotional adjustment of college students, as evaluated principally by psychometric technic, and success in dieting was studied by Summerskill and Darling.[64] A significant relationship was found, using pounds lost through dieting and ratings of acceptance of controlled dieting as the criteria. The authors noted that obesity can be associated with states of emotional adjustment varying all the way from the essentially normal to the seriously disturbed.

The need for effective methods for changing food habits so as to lose weight and maintain proper weight continues to call for the participation of social scientists. Sussman[65] studied the formation, collapse and reconstruction of a group called "The Calorie Collectors." The objective of the organization was to help its members to lose weight. Its equivalents, stimulated in part by the success of the Alcoholics Anonymous, sprang up in different parts of the country. While such a "movement" poses undeniable dangers, and the field of weight reduction does not lack exploiters, the group technic of weight reduction should not be ignored. Sussman[66] outlined in some detail the points to be considered in working with organized local groups of overweight individuals and helping them to develop effective programs of weight reduction and control.

FOOD FLAVOR AND ACCEPTABILITY

The control of flavor of foods and beverages is the concern of the food technologist. Yet, the problem has important implications for the nutritionist. The most nutritious cooked breakfast cereal or Army rations will do no good for personnel of the Armed Forces or anyone unless consumed. The appraisal of flavor, be it in terms of a more neutral, descriptive analysis or in reference to food acceptability, is a task that involves behavior. Work in this area cuts across a wide spectrum of problems and methods, from psychophysics and psychophysiology (psychochemistry, if you wish) to the psychology of personality and education, with advertising thrown in for good measure.

On account of far-reaching practical implications, the problem of flavor has attracted the attention of the food industry, of the Armed Forces, and of governmental agencies. The Quartermaster Food and Container Institute (Chicago) arranged a symposium on food acceptance methodology.[67] The proceedings are the best source of information on this subject, with speakers drawn from the ranks of academic institutions, industrial laboratories, United States Department of Agriculture, and the Quartermaster personnel.

Flavor is a complex sensation, with taste, aroma and "feeling" as the three categories of components. The problems of odor in reference to fundamental aspects (nature of the olfactory process), subjective and objective measurement technics and industrial applications, were considered *in extenso* in a symposium held under the auspices of the New York Academy of Sciences, with A. R. Behnke as general chairman.[68] The essentially interdisciplinary character of odor research was stressed by considering it from the points of view represented by a physicist, a chemist, a physiologist, and a psychologist.

The "profile method" of flavor analysis, combined in A.D. Little's Flavor Laboratory with physiochemical studies in which an attempt is made to isolate and identify the crucial flavor components, was described in detail by Caul.[69] The profile of a product is determined by a specially trained panel of taste-testers in terms of five characteristics of flavor: overall impression ("amplitude") of aroma and flavor, perceptible aroma and flavor factors, intensity of each factor, the order in which the factors are perceived, and after-taste.

At times only a single, narrow aspect of flavor, such as the bitterness of orange juice,[70] is of interest. A simplified method for detecting flavor changes in vegetables after being treated with pesticides was presented by Kramer and Dittman.[71]

A LOOK INTO THE CRYSTAL BALL

We have surveyed briefly and incompletely some of the recent developments in the complex field of studies on nutrition and behavior. How about the future? What are the im-

portant problems? What are the promising methods?

"Importance" can be assessed in terms of two types of criteria, theoretic and practical. Theoretically, facts and ideas derive their importance from opening new horizons and closing gaps in our knowledge. Only the specialist, intimately familiar with the status of his narrow segment of the field being surveyed, could attempt to chart the future course of research. While applied research can be planned readily, fundamental advances, by their very nature, are not simply a matter of increased manpower and improved technical facilities. It will be some of the practical aspects, rather than potential theoretic developments, that will be primarily considered here.

The practical criterion, in terms of which—in the last analysis—all of biologic research must be evaluated, is the contribution to man's health, including mental health, and productivity. Thus the questions of food additives or pesticides must be appraised, first of all, in terms of possible toxic and carcinogenic effects. However, the effect, if any, on the taste of vegetables, fruit and other foods cannot be neglected.

The food industry will remain interested in problems of flavor and the more general problem of food acceptance. Flavor control is as essential to the standardization of a product as the food composition. There is plenty of room for further advancement of fundamental knowledge of the "chemical" senses of gustation and olfaction. We agree with Wenger, Jones, and Jones[72] who stated: "one of the fascinating aspects of the chemical senses is the paucity of knowledge concerning them and the continued expectation of living on the brink of great discovery." Relations between chemical composition and the sensory effects of chemical compounds are inadequately understood at present.

Controlled investigations carried out in the laboratory indicate clearly that deficits of calories and of essential nutrients, especially of some of the vitamins of the B-complex, notably thiamine, have profound impact on both components of work performance, i.e., motivation and work capacity. In view of the large areas of the world plagued or threatened by undernutrition, the degree and the nature of adaptation to undernutrition is one of the most intriguing problems.[72a] Impact of improved nutrition is its natural and important complement.

As a result of tremendous technologic advances in food production, processing and distribution, combined with a rise in purchasing power and widespread nutrition education, outright nutritional deficiencies in such countries as the United States are becoming very rare. Has, then, the nutritionist nothing more to say or to do? Yes, he does. He has, unfortunately, more to do than he has to say at present.

The challenge presently facing workers in medicine and public health, including the nutritionists, is the large category of "degenerative," non-infectious diseases with ischemic heart disease and cancer as the leading causes of death in this country. No promising leads on the potential role of nutrition in the etiology and prevention of carcinogenesis in man appear to be available. In the field of heart disease attention has been given principally to overweight, frequently regarded as an important factor in the development of coronary heart disease. The survey of the available evidence is inconclusive. It was noted that additional research is needed to assess more precisely the role of "overweight," "obesity" and the individual differences in skeletal proportions and the distribution of soft tissues.[73]

Weight reduction undertaken as a preventive or curative measure, on an individual or group basis, is a fruitful field of research and application for the clinical psychologist, psychiatrist, and social psychologist. As a valuable warning, and counterbalance to the high-pressure salesmanship of some commercial, medically unsupervised weight reducing establishments, untoward reactions to weight reduction among certain obese persons were pointed out by Stunkard.[74] This confirmed Bruch's findings that acute emotional disturbances may be precipitated by attempts at weight reduction. Semi-starvation, even in the overweight individual, can not be prescribed in an off-hand manner. Seeing the

problem as a psychiatrist, Bruch[75] entitled the fruit of 20 years work: "*The Importance of Overweight.*"

Even if we could be unreservedly enthusiastic about weight reduction in obese but otherwise normal individuals and if we were to accept as representative the excessive cardiovascular mortality among insured overweights (50 per cent above the death rate among "standard risks"), the removal of overweight would not bring about a *striking* reduction in the burden of heart disease. It would still leave the U. S. coronary death rate among middle-aged adults distressingly high in comparison with that in some other parts of the world.

While a number of problems, especially those concerned with blood coagulation[76]—as distinct from factors regulating the level of blood cholesterol, await further exploration, the richness of diets, particularly in respect to animal fats[77] appears to be the principal biologic factor differentiating areas of high and low mortality due to coronary heart disease.[78] It may be that food habits, with special emphasis on fat intake, and the attempt to modify these habits in the light of the accumulating evidence of the health significance of dietary fats, will represent the most important issues in studies on nutrition and behavior during the next ten years.

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Editorial

A "Pickwickian" Syndrome

Recently an unusual clinical syndrome has become apparent. In a number of case reports[1–4] patients have been described who showed extreme obesity, polycythemia, cyanosis and cardiopulmonary failure. Because of the frequency of somnolence Burwell and associates[1] noted the similarity between this syndrome and "Mr. Wardle's boy Joe" in Dickens' "The Pickwick Papers."

In essence this syndrome consists of massive obesity (250 to 400 lb) and polycythemia secondary to a reduction in alveolar ventilation because of the excessive corpulence. The thoracic cavity is "crowded by fat,"[2] the total lung volume is reduced, the breathing is shallow and Cheyne-Stokes respiration and cyanosis may be present. Physiologically, the pathogenesis may be described as follows: mechanical restriction because of obesity results in inadequate alveolar ventilation. This leads to a low alveolar oxygen and a high carbon dioxide. This in turn leads to hypoxia and hypercapnia. These in turn produce periodic breathing, somnolence and the polycythemia resulting from anoxia.

The amount of work necessary to keep the CO_2 pressure continuously at normal levels is so great that the body compromises and allows the CO_2 to rise. A somewhat analogous situation occurs in patients with respiratory poliomyelitis, obstructive emphysema or kyphoscoliosis.[3]

The heart may fail under these circumstances. Carroll[3] has described three patients with right-sided congestive failure and right-axis deviation of the electrocardiogram: autopsy of one of these cases revealed no cardiac abnormality except dilation and hypertrophy of the right auricle and ventricle. The patient described by Burwell *et al.*[1] had peripheral edema, increased venous pressure, a large liver and incomplete right bundle branch block.

The polycythemia is of variable degree. Weil and Prasad's[2] patients had initial hemoglobin values ranging from 18 to 21 g/100 ml and a hematocrit ranging from 53 to 73 per cent. The estimated blood volume in two patients was 6,400 and 9,900 ml before therapy. Unlike polycythemia vera, however, there are no changes in white cell or platelet counts. Bone marrow examination may reveal mild erythroid hyperplasia, although diffuse hyperplasia (involving the myeloid and megakaryocytic series) is not observed.

Of special interest is the improvement in the clinical picture on weight reduction. For example, one patient lost 40 pounds in three weeks on an 800 cal diet.[1] The total vital capacity increased from 1.6 to 4.2 liters, alveolar ventilation from 2.7 to 4.4 lit/min. The oxygen saturation of arterial blood rose from 80 to 98 per cent. There was evidence that, on admission, when the patient had a high arterial pCO_2, the sensitivity of the respiratory center was far below normal. After weight reduction the patient responded in an essentially normal manner. In another patient a weight loss of 36 pounds led to a fall in hemoglobin from 18.6 to 12.9 g/100 ml and a fall in hematocrit from 60 to 40 per cent. In general, similar results were obtained in the other cases studied before and after weight reduction.

The syndrome is probably not at all rare. Since the condition seems to be promptly reversed by weight reduction it becomes even more a responsibility of the clinician to be aware of the ill effects of obesity,—here affecting the cardiopulmonary and hematologic systems.

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The Spirit of Inquiry

"The spirit of inquiry is admirable if it is really inquiry and not uncritical novelty worship. It is right that we should examine and consider every new thing that is presented to us, but not necessarily right that we should adopt it. Most new things turn out in the end to be wrong. When presented with a new project for acceptance, we should first ask: 'Is it reasonable?' Then, 'Is it really new? Has it, or anything like it, been tried before? If so has it failed, and why? Was the failure due to some inherent defect, or to some circumstances that can now be remedied? If it is reasonable but yet untried, can it be tried without risk? If there is a risk, how can that risk be eliminated or minimised? Are we justified in a full-scale trial, or should we first try a pilot experiment? Can the experiment be done first on ourselves?' "
—Sir Heneage Ogilvie. *Lancet* 1: 115, 1956.

Diet Therapy

THE COST OF AN ADEQUATE DIET

By BETTY JANE JOHNSTON, M.S.*

FOOD is the item which takes the greatest proportion of the family budget at a low or moderate income level. The amount of money a family can spend on food, and the type of food this sum buys are both important factors in determining dietary adequacy.

LOW AND MODERATE COST PLANS

The Recommended Dietary Allowances of the Food and Nutrition Board, National Research Council[1] provide a practical guide for planning normal and therapeutic diets,[2] and can also serve as a basis for determining the cost of an adequate diet. These recommended allowances have been translated by the Human Nutrition Research Branch of the United States Department of Agriculture into the kinds and quantities of foods that will furnish a nutritionally adequate diet at a low and moderate cost level.[3] These food lists have been detailed for each of the age and activity groups listed in Table I.

A U. S. Department of Agriculture publication[4] describes the two cost levels as follows:

"The plans differ in relative quantities of foods from the different groups and in choice of foods within a group. The low-cost plan relies heavily on the cheaper food groups: potatoes, dry beans and peas, flour and cereals. Also this plan is based on selection of the cheaper foods within the groups, for instance, the less expensive cuts of meat and the lower priced vegetables and fruits.

"The moderate-cost plan allows for larger quantities from the more expensive food groups such as meat and eggs. It allows also for some of the higher priced cuts of meat and a few out-of-season foods.

"Menus made from the quantities suggested in the low-cost plan will be simple. They will include foods requiring a considerable amount of home preparation and will call for skill in cooking to make varied and appetizing meals. They will have more cereal products, potatoes, and dry beans and peas. On the other hand, the moderate-cost plan will allow for menus with greater variety, some frills, and less home preparation. Although neither plan allows for much waste in food preparation, the moderate-cost plan has slightly more leeway than the low-cost."

BUDGET ALLOWANCES FOR FOOD

The following table shows the estimated cost of one week's food at these two levels when food is prepared and served at home. The weekly cost of food for a specific family can be estimated from this table since costs are given for individuals of different ages and degrees of activity. Such cost estimates are usually made in June and December of each year, with interim adjustments during periods of rapid price change.

Variation in food costs amounts to well over 100 per cent between the highest and lowest categories, indicating the effect of sex, age and activity characteristics on cost.

Obviously, the number in the family group also affects food costs. The small family usually cannot buy and prepare its food as economically as can a large family. For this reason, the following additions to the esti-

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TABLE I

Estimated Cost of One Week's Food (October 1956)[5]
(Average Prices in 46 Cities)

Age and activity groups	Low-cost adequate diet	Moderate-cost adequate diet
Children:		
1–3 years	$3.00	$3.75
4–6 years	3.75	4.50
7–9 years	4.50	5.25
Girls:		
10–12 years	5.00	6.00
13–15 years	5.50	6.50
16–20 years	5.25	6.50
Boys:		
10–12 years	5.50	6.25
13–15 years	6.25	7.75
16–20 years	7.00	8.50
Women:		
Sedentary	5.00	6.00
Moderately active	5.50	6.75
Very active	6.00	7.75
Pregnant	6.50	7.75
Nursing	8.00	9.00
60 years or over	5.00	6.00
Men:		
Sedentary	5.50	6.75
Physically active	6.00	7.75
Doing heavy work	7.50	9.75
60 years or over	5.50	6.50
Per capita	5.50	6.75

mated weekly cost are suggested: for an individual living alone, add 35 per cent; for two in the family, add 20 per cent; for three in the family, add 10 per cent. For families of six or more a reduction in food costs is often possible because of the economies possible when buying and cooking in larger quantities.

The allowance for food granted to Public Assistance recipients varies among the states. Practically all of the food budgets planned for this type of case use the "low-cost food plan" of the U. S. Department of Agriculture. Usually the amount allowed is based on local pricing of the foods on this list. However, limited funds, and often administrative simplification, resulting in a rigid system of allowances without differentiation for age, sex and activity characteristics, mean that the actual allowance is different from the amount obtained by pricing. This may result in hardship for families whose composition varies from the "standard" family of four persons or whose health and activity require special food consideration.

Using the median allowance of seven industrial states,* an old age assistance recipient might receive $28.15 per month for food; a family consisting of sedentary father, moderately active mother, boy 13 years of age and girl 7 years of age might receive $83.45 per month for food. These median amounts approach the estimated cost of providing a low-cost adequate diet, but would fall below this where the family group includes several teenagers, active adults, and/or a pregnant or lactating woman.

It is possible to provide the recommended dietary allowances with food quantities which can be purchased for 15 to 20 per cent less than those in the low-cost plan. However, adequate diets at lower costs tend to deviate from normal diet patterns, requiring the cooperation of the entire family in accepting less variety at mealtime, larger amounts of grain products, dry beans and peas, and potatoes, and much smaller quantities of meat, fish, poultry and eggs. For a family to maintain an adequate diet at this level for any extended period of time would be difficult without expert guidance in food management.

In general, extra money spent for food is apt to provide a more varied diet, and therefore a more nutritious diet. A study of rural, low-income families in the North Central States[6] indicates that the households of homemakers over 60 years of age had poorer diets. Older homemakers tended to limit their food selection, and those who used relatively few foods during a week were likely to have poorer diets than those making a wider choice.

The quantities of food per person in the diet of these low-income families compared with those from the "low-cost food plan" suggest where improvement might be made. Older families used much less milk, and were more likely to omit altogether an important food group such as citrus fruits and tomatoes, leafy, green and yellow vegetables, or relatively

* Illinois, Indiana, Massachusetts, Michigan, New Jersey, New York and Wisconsin.

economical sources of protein such as legumes.

Many families are not especially restricted in the amount of money they can spend for food, but this is not in itself a guarantee of an adequate diet. Care must still be taken to insure ample amounts of all the nutrients by including sufficient quantities of such foods as milk and milk products, fruits and vegetables.

CHARACTERISTICS OF DIETS AT FOUR LEVELS OF COST

The manner in which the quantities of various food groups may be increased or decreased is illustrated in Table II. These food needs would vary for different age and activity categories.

liver at 13 cents on the low-cost diet, or calf liver at 37 cents per serving on the liberal-cost diet. The lower grades and the cheaper cuts of meat can be used on the lower cost levels, and the better grades of rib roasts and steaks on the liberal level. Adjustments of this type are shown in Table III.

COST CONSIDERATIONS FOR THERAPEUTIC DIETS

When a therapeutic diet is prescribed for a patient by a physician, the cost of such a diet may or may not be higher than that for a person in good health.[7] When dietary modification can be made without seriously altering the normal diet, increased food costs should not be necessary in most cases. Qualitative

TABLE II

Weekly Food Needs (As Purchased) for a Family of Four*

Food group	Restricted[4] diet	Low-cost[3] diet	Moderate[3] cost diet
Leafy, green, and yellow vegetables	7 3/4 lb	9 lb	11 3/4 lb
Citrus fruit, tomatoes	6 1/4 lb	8 1/2 lb	10 1/4 lb
Potatoes, sweet potatoes	14 lb	12 lb	10 1/2 lb
Other vegetables and fruits	5 1/4 lb	7 1/4 lb	12 1/4 lb
Milk (or equivalent in cheese, dry milk)	18 1/2 qt	18 1/2 qt	20 1/2 qt
Meat, poultry, fish	3 3/4 lb	7 1/2 lb	10 1/4 lb
Eggs	15	20	28
Dry beans, peas, nuts	1 7/8 lb	1 1/4 lb	5/8 lb
Flour, cereals†	14 1/4 lb	13 lb	11 lb
Fats and oils	2 3/4 lb	3 lb	3 1/8 lb
Preserves, sugar, syrups	2 3/4 lb	3 lb	3 3/8 lb

* Father, sedentary; mother, moderately active; boy, 13 years; girl 7 years old.
† 1 1/2 lb bread equal 1 lb flour, cereal.

In general, the quantity of milk and milk products should not be changed greatly, regardless of the amount to be spent for food. The greatest adjustments to a lower cost level can be made by reducing the quantities of meat, poultry and fish somewhat, and also the group described as "other vegetables and fruits," and increasing the potato and cereal intake. Within any food group there are both expensive and inexpensive sources of the important nutrients. The cost of the meat, poultry and fish group depends on the specific kind of meat, poultry or fish priced, and the division of the total poundage among them. For example, when liver is used, it might be lamb liver at 10 cents per serving on the restricted diet, beef

changes, such as variations in the consistency and digestibility of food should be obtainable at a cost similar to the cost of an adequate diet for a well person. Changes with respect to the quantity of one or more nutrients may mean that the patient must seek the less expensive sources of some nutrients, unless food costs are to be greatly increased. This becomes a problem in nutritional education. For a patient who has a low income and especially one with a fixed food allowance, some education as to the relative costs of different sources of a nutrient is essential—for an increased food allowance for one person may result in either an inadequate diet for other members of the family, or money taken away from other basic

TABLE III

Characteristics of Adequate Diets at Four Levels

	Restricted	Low	Moderate	Liberal
Estimated cost per week: for family of four (school age children)	$17.50	$21.50	$26.00	—
Meat, poultry, fish, eggs, dry beans and peas, nuts	Very small quantities of meat, poultry, fish and eggs Lower grades and cheaper cuts Inexpensive variety meats Much larger amounts of dry beans and peas, lentils	Small quantities of meat, poultry, fish, eggs Lower grades and cheaper cuts Inexpensive variety meats Large amounts of dry beans and peas, lentils	Larger quantities of meat and eggs Some higher priced meats	Larger quantities of meat and eggs Higher grades, more expensive cuts
Leafy, green, yellow vegetables, citrus fruits, tomatoes	Cheapest fruits and vegetables in season More potatoes Canned tomatoes or juice when citrus fruits are high Canned citrus juices when cheaper than fresh fruit Cheaper grades of canned products	Lower priced fresh fruits and vegetables in season More potatoes	Fresh fruits and vegetables in season A few out-of-season foods	More variety in fresh fruits and vegetables Use of more expensive and out-of-season ones
Milk, milk products	Evaporated and non-fat dry milk when cheaper than fluid milk	Evaporated and non-fat dry milk when cheaper than fluid milk		
Bread, flour, cereals	Much larger quantities Cereal products as extenders No expensive ready-baked items	Larger quantities Cereal products as extenders No expensive ready-baked items	Smaller quantities	More expensive ready-baked items
Other characteristics	Much home preparation of food Food served at home Fewer foods in one meal with larger servings of these	Home preparation of food Food served at home Fewer foods in one meal with larger servings of these	Some ready-to-serve and partially prepared foods A few meals eaten away from home More items in one meal	More ready-to-serve and partially prepared foods More meals away from home

needs such as shelter and clothing. A nutritionist, dietitian, or nurse with experience in budgetary planning, as well as in construction of therapeutic diets, can provide invaluable assistance. For those who must rely on published materials, the planning guides listed at the end of this article are reliable, readily available and inexpensive.

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PLANNING GUIDES

Human Nutrition Research Branch, U. S. Department of Agriculture, Washington, D. C.
Helping Families Plan Food Budgets, Misc. Pub. No. 662, 1950
Food for Two

Food for the Family with Young Children, Bulletin G-5
Food for Families with School Children, Bulletin G-13
Food Guide for Older Folks, Bulletin G-17
Nutrition Up to Date Up to You, Reprinted from Home and Garden Bulletin No. 1, Family Fare, Separate 1
Budget Standards for Family Agencies in New York City, New York Budget Council, 105 East 22nd St., New York City
Chicago Standard Budget for Dependent Families, Budget Committee of the Family and Child Welfare Division, Chicago Council of Social Agencies, 344 S. Dearborn St., Chicago, Ill.
Family Low-Cost Budget Guide, Health and Welfare Council, 311 South Juniper St., Philadelphia 7, Pa.
Guide to Limited Family Incomes in Pittsburgh and Allegheny County (see reference 7)
The Minimum Family Budget, Visiting Nurse Association of Boston, 137 Newburg St., Boston 16, Mass.

Reviews of Recent Books

Biochemical Individuality, by Roger J. Williams, John Wiley & Sons, Inc., New York, 1956, pp. 214, $5.75.

No one denies that it is necessary to manufacture synthetic pictures of disease which we must compare with a synthetic picture of normality. But it takes much wisdom and much experience to realize that in the final analysis the notion of *the normal* as an entity and the concept of disease as a classic textbook entity are both figments. In times gone by, when physicians were not so bewildered by choosing what specific to use, since there were so few of them, it was possible for wise doctors to concentrate more on the individual. There was then much thought and action based on ideas of diathesis, disposition and temperament. Much more attention was devoted to the physiognomy of disease as it was modified in each sick person. To some extent these views of our medical forefathers were weakened by artificial systems of nosography in which single causes were emphasized to the exclusion of the tremendous importance of individual variations of response, resistance, susceptibility, and so on.

The notion of physical individuality has become widely accepted with studies of body type, with emphasis on such qualities as maleness and femaleness, and with reference to susceptibility to disease. In 1916, my father, R. B. Bean, published one of the first documented studies of the variations in frequency and severity of particular diseases among individuals of different anthropologic types. He found that there were some well-marked tendencies which might have some predictive value for the clinician. Thus Hippocratic intuition began to get objective verification. Only with the vast proliferation of information obtained by chemists have we faced the problem of conformity or individuality in the biologic, biochemical, and enzymatic constituents and characteristics of various people. Roger Williams, who has emphasized what he calls the genetotrophic concept of disease, has amassed a great deal of evidence, much of which has been collected in his own laboratory, which suggests very strongly that just as no two fingerprints are alike, so we all seem to differ, one from another in our biochemical patterns. These arrangements seem to result from genetically determined biochemical processes.

As an example of an inevitable correlary on these facts, we may confront the problem of "vitamin requirements." For a point of argument, let us assume there are finite and specific vitamin requirements at a minimal level for safety and, higher, at an optimal level for "ideal" health. Let us assume that all the environmental variables such as climate, activity, pregnancy, lactation, growth, are kept constant in a sizeable population. Still the requirements for any particular vitamin may vary many, many fold among different people, and in the same person perhaps from time to time. Likewise most persons might have some high, some middling, and some low requirements, though conceivably rare creatures might have low requirements all across the board, and others all high requirements. The impossibility of setting up an idealized list of requirements satisfactory for everyone is immediately apparent.

This thesis, which seems reasonable, but which requires much further verification, is enormously important in clinical medicine for it emphasizes again that each problem must be individualized, that standard doses of most medicines are wasteful for some patients, and unsafe for others, and that we cannot practice properly unless we know enough of the pharmacologic effects to adjust our treatment to the individual requirement for various patients under varying circumstances. The same is true for food and for vitamins. In a time of plenty we can be wasteful, and advise diets adequate for almost everyone. But in the present pressure for space and food as a global problem, ultimately we may need to study each person's individual requirements for many essential nutrients, and tailor his eating to suit his needs rather than his tastes. But probably such a custom-built approach can be afforded only by those who really don't need it. Roger Williams, in this searching book gives us much to think about, for we can never solve problems until we recognize them and face them.

WILLIAM B. BEAN

ABC für Zuckerkranke, by F. Bertram, Georg Thieme Verlag, Stuttgart, Germany, 1956, pp. 84, D. M. 4.20, $1.

This little booklet by Professor Bertram, a well known clinical expert in diabetes in contemporary German medicine, is written for the diabetic patient. It contains three interesting features which are somewhat different from the recommendations given to the diabetic patient in this country.

(1) Dr. Bertram stresses a relatively rich carbohydrate, normal-protein and low-fat diet. Generally, he does not allow more than 70 to 80 g of fat per day. He also restricts cholesterol-rich foods, especially eggs. His emphasis on a low-fat diet seems very well justified

considering the interesting experience that diabetic patients did remarkably well in Europe during the war years when they depended to a large extent on carbohydrates in the food available as potatoes, rye bread and vegetables, since little fat and protein were available. Nowadays diabetes in Germany is rapidly increasing as it is in every country with high living standards—a fact for which the author blames mainly the high-fat content of the modern diet. Dr. Bertram's dietary regimen is in the tradition of the famous v. Noorden school.

(2) The author's guide for the diabetic patient includes for the first time a discussion of the new orally active blood-sugar lowering sulfa-like drugs. His opinion on this subject is apparently an optimistic one which may be justified by his experience with these drugs. He stresses the fact, now completely accepted, that these drugs are most useful in the older obese patient, suggesting that some insulin must still be produced if the drug is to be effective. Nevertheless, in the opinion of the reviewer, one should not forget that one or two years is a relatively short period for a thorough evaluation of the possible therapeutic value and of the possible inherent toxicity of a new therapeutic principle.

(3) Another section deals with the benefit of muscular activity for the diabetic. That such activity is indeed an excellent therapeutic adjuvant in the treatment of diabetes is supported by recent experimental findings. The very personal point of view, expressed by Dr. Bertram in this little booklet, should stimulate the physician who has to deal with diabetic patients, to compare critically a regimen now widely followed in Germany with that which presently prevails in this country. ERNST HELMREICH

The Biological Basis of Human Freedom, by T. Dobzhansky, Columbia University Press, New York, pp. 135, $2.95.

The author of this significant book is an eminent biologist and geneticist. In 1954 he delivered the Page-Barbour lectures at the University of Virginia which comprise the basis for the essays in this short book. The style is forceful and lucid. The text is challenging and stimulating.

Early in the discussion Dobzhansky states that there is no such thing as a purely inherited or a purely environmental trait. This seems amply confirmed by a wide variety of data from numerous disciplines. Perhaps the section with the widest appeal to the general reader is the one entitled "Heredity as a Basis of Culture." Here the author shows that "human evolution is a singular product of interaction between biology and culture." In the chapter "Who Is the Fittest?" he indicates that natural selection does not necessarily favor what we may regard as desirable. Later in an important section dealing with ethics and biology he concludes that the ability of man to choose freely between ideas and acts is one of the fundamental characteristics of human evolution. Freedom may be the most important of all the specifically human attributes. Furthermore, ethics emanate from freedom and are unthinkable without freedom.

Thus a thinker and scientist views the role of man partially bound by his genes and enclosed in his environment. It is a balanced logical appraisal and one badly needed in these days of scientific speed. S. O. W.

Experimental Methods for the Evaluation of Drugs in Various Disease States, edited by B. N. Craver, *Ann. N. Y. Acad. Sc.* 64: 463–732, (Nov.) 1956, $3.50.

A conference on experimental methods in drug evaluation was held by the New York Academy of Sciences in March 1956. Twenty-one papers were presented which were divided into the following general headings: collagen diseases, angina pectoris, cardial arrhythmias, atherosclerosis, and disorders of the central nervous system.

The contributors in general are highly experienced workers in their fields. Nevertheless, the quality of the presentations varies considerably. Most of the writers discuss the pros and cons of specific technics used in their work. These are important and necessary matters. But this reviewer would have preferred a more thoughtful analysis of the principles of drug evaluation. The book contains much valuable information which should be of special interest to investigators working directly in the fields discussed. They will find therein many valuable hints and suggestions. Although some of the authors seemed anxious to review their own work and re-emphasize their views, the objective reader will benefit by a critical reading of these important contributions. S. O. W.

Books received for review by THE AMERICAN JOURNAL OF CLINICAL NUTRITION are acknowledged in this column. As far as practicable those of special interest are selected, as space permits, for a more extensive review.

British Medical Bulletin, Physiology and Pathology of the Kidney, Vol. 1, January 1957, pp. 74, $3.25.

Guide to Medical Writing by Henry A. Davidson, The Ronald Press, New York, 1957, pp. 338, $5.00.

Liver, Biliary Tract and Pancreas, edited by Frank H. Netter, Part III of Volume 3, Digestive System, The Ciba Collection of Medical Illustrations, Ciba, Summit, N. J., 1957, pp. 165, $10.50.

The Importance of Overweight by Hilde Bruch, W. W. Norton, New York, 1956, pp. 438, $5.95.

Essentials of Nutrition, 4th edition, by Henry C. Sherman and Caroline S. Langford, MacMillan, New York, 1957, pp. 505, $4.90.

Advances in Food Research, Vol. 7, by E. M. Mrak and G. F. Stewart, Academic Press, New York, 1957, pp. 404, $9.50.

Abstracts of Current Literature

NUTRITIONAL ASPECTS OF DIABETES MELLITUS

Nutritionally oriented physicians are keenly interested in diabetes, a disorder providing them with a new investigative challenge with each patient brought under observation. While many efforts have been made to classify diabetics into obese or non-obese; labile or stable; insulin-sensitive or resistant, we must finally recognize that these definitions are inadequate. Diabetes, even in the obese, mild case, is a fluctuating and dynamic process. A patient with nothing more than an abnormal glucose tolerance test when first studied may after several years be found to require substantial amounts of insulin. On the other hand, striking reductions in insulin requirements are occasionally observed after periods of control and in association with reduction of obesity. One of the dangers involved in the concept that the obese patient, not requiring insulin, is a "mild" case is the tendency for this group to manifest hyperlipidemia and degenerative vascular lesions if care is not taken to avoid asymptomatic hyperglycemia.

A Comparison of Obese and Nonobese Diabetic Subjects. I. Murray and I. Wang. *Diabetes* 5: 49, 1956.

The authors point out that from a clinical standpoint the obese or "lipoplethoric" diabetic differs in many respects from the nonobese insulin-deficient diabetic. One thousand patients from Victoria Infirmary in Glasgow were classified into two main groups. The obese group consisted of all patients who were 20 per cent or more above ideal weight and those who had never been heavier than the ideal weight. As is usual, classification and definition of ideal weight was difficult due to overlapping.

The age of onset of diabetes was strikingly different, in that of the obese patients 94 per cent were 40 years of age or more when diabetes was detected, whereas 52 per cent of the nonobese were under forty at the onset. Females dominated the obese groups 5.13:1, while in the nonobese the ratio was practically 1:1. Ninety-two per cent of the nonobese group required insulin, while in only 17 per cent of the obese group was this deemed necessary. The development of ketosis was apparently not studied in detail, although the authors say that six obese patients of a total of 337 "showed a definite liability to develop diabetic ketosis." The incidence in the nonobese group is not given. The family incidence and inheritance of obesity and diabetes was also studied. The obese group of diabetics had a remarkable family history of obesity; 67.7 of the patients having obese, though nondiabetic, relatives. Both obese and nonobese groups have a family history of diabetic relatives in approximately the same proportion, 27.3 per cent for the obese and 25.1 per cent for the nonobese.

The authors did not define what they classify as "diabetic" and this would seem to be quite important in this type of investigation. This is a useful type of study and serves the purpose of again pointing out a definite difference between the obese and nonobese diabetic.—K. R. CRISPELL

While it is possible that elevated cholinesterase levels are associated with obesity, it would be of interest to note the status of liver function in those with high serum levels of this enzyme. Some obese patients as well as some diabetics manifest hepatic lipidosis which may influence the serum cholinesterase values.

Serum Cholinesterase Levels in Diabetes Mellitus. R. H. S. Thompson and J. R. Trounce. *Lancet* 1: 656, 1956.

The serum cholinesterase has been shown to be raised in diabetes mellitus, but it has been suggested that the raised levels may be related, not to the diabetes *per se*, but to the obesity which often accompanies it.

In this study serum cholinesterase was measured in 58 healthy adults, 25 of them obese, and 50 outpatient diabetics, 25 of whom were also obese. The cholinesterase levels (measured by the method of Ammon and quoted as μl of CO_2/ml of serum/minute) were as follows: nonobese healthy adults—76 (range 53–102); obese nondiabetics—102 (60–151); nonobese diabetics—81 (51–120); and obese diabetics—107 (43–175).

It appears therefore that the raised level in diabetics is in fact associated only with accompanying obesity. The possibility is discussed that this pseudo-cholinesterase may be concerned with some aspect of fat metabolism.—F. E. HYTTEN

For many years diarrhea has been recognized as an occasional complication of diabetes mellitus. This condition is generally regarded as an autonomic neural disorder and is invariably associated with evidences of peripheral neuropathy. Like all other diabetic complications involving the nervous system, no adequate explanation for its occurrence has been discovered. I (C.R.S.) have seen the clearing of this problem with careful diabetic control on a high-protein, low-residue diet.

Steatorrhea Complicating Diabetes Mellitus with Neuropathy. Report of Cases Without Apparent External Pancreatic Insufficiency. K. G. Berge, E. E. Wollaeger, D. A. Scholz, E. D. Rooke, and R. G. Sprague. *Diabetes* 5: 25, 1956.

Disturbances of gastrointestinal function have frequently been observed in association with diabetes mellitus. These include gastric atony and dilatation, postprandial abdominal cramping, severe constipation, and intractable diarrhea characterized by watery stools, nocturnal exacerbations, and fecal incontinence. The authors report on six cases of intractable steatorrhea complicating long-standing diabetes mellitus with neuropathy. The symptoms of diarrhea characterized by postprandial and nocturnal exacerbations and by nocturnal fecal incontinence were similar to those previously reported in cases of diabetic diarrhea. They point out that there was no evidence of other disorders characterized by steatorrhea such as nontropical sprue or Whipple's disease. In all six cases there was definite evidence of neuropathy, presumably diabetic in origin.

A search for the basis of the steatorrhea was made in all cases. It was impossible to establish the presence of external pancreatic insufficiency. An autopsy on one patient showed no evidence of destruction or obstruction of the pancreatic acini. The possible etiologic role of autonomic neuropathy involving the gastrointestinal tract is discussed.

This is an interesting observation and serves to alert us to one more serious complication of long-standing diabetes mellitus.—K. R. CRISPELL

The sustained hyperosmotic effect of continuous hyperglycemia upon cellular fluid and electrolyte balance may be responsible for cataract formation through changes in lenticular proteins. Such a concept would provide a cogent basis for the more scrupulous control of diabetes. A somewhat different explanation for cataract formation is offered in the following work. However, the same conclusion regarding diabetic management is warranted.

Diabetic Cataracts. A Review of Experimental Studies. J. W. Patterson. *Diabetes* 5: 93, 1956.

This is an excellent review of the present status of the experimental work relating to diabetic cataracts in rats. The author discusses in an orderly fashion (1) the relationship of the severity of diabetes to cataracts; (2) diabetic factors that influence cataracts; (3) evidence for a theory concerning the development of cataracts.

Following the production of diabetes in the rat, with alloxan, cataracts will appear if the blood sugar is maintained above 250 mg/100 ml. The time required bears an inverse relationship to hyperglycemia. These cataracts can be prevented by insulin administration. A high-fat diet, fasting, and phlorhizin, all of which lower blood sugar, will also prevent or delay the onset of these cataracts. This suggests that hyperglycemia plays a direct role in the production of cataracts. However, unilateral carotid ligation in diabetic rats does not affect the side on which cataracts are first observed. This then questions the hypothesis that hyperglycemia is directly responsible for the production of diabetic cataracts.

The author advances the theory that in the absence of insulin the uptake of glucose by the lens is impaired. Since the lens depends on glucose for a major portion of its energy, the total available energy is lowered beyond the critical point that is necessary for maintaining transparency. A decrease in available energy could produce cataracts by stopping the synthesis of glutathione, enzymes, proteins, other structural compounds, or by blocking the maintenance of a water and electrolyte balance. He furnishes evidence to support this hypothesis by presenting studies of glucose uptake on isolated lenses and by studies with diets that supply energy yielding substances other than glucose.

The author adequately summarizes the work to date as follows: "The study of one of the complications of diabetes provides evidence indicating that at least one tissue in the body degenerates in uncontrolled diabetes because it is unable to absorb glucose and because alternate nutrient substances are not available in adequate quantities. The provision of a diet containing substances that do not require insulin for utilization prevents this tissue degeneration."—K. R. CRISPELL

Effect of High Fat, Fructose and Casein Diet on Diabetic Cataracts. J. W. Patterson. *Proc. Soc. Exper. Biol. & Med.* 90: 706, 1956.

Experiments were carried out in order to decide whether hyperglycemia as such or the particular source of energy causes cataracts in alloxan-diabetic rats. For this purpose, a diet was fed to alloxan-diabetic rats (Sprague-Dawley males) which did not lower the blood sugar level but provided energy from fructose rather than glucose. Young rats were used and the experimental diet consisted of 50 per cent fructose, 25 per cent corn oil, and 25 per cent casein fortified with vitamins and minerals. Cataracts did not develop and body growth was accelerated over that of controls fed a stock diet. Apparently cataract formation may be prevented in diabetic animals without insulin if energy derived from sources other than glucose is made available. Cataracts may thus result from the inability to obtain adequate energy from glucose in the absence of insulin.—M. SILBERBERG

The excellent results achieved by Pederson are now being duplicated in many clinics in this country. The fetal survival in diabetic pregnancies is nearing 90 per cent without sex hormone treatment when careful diabetic supervision and early hospitalization is enforced.

Foetal Mortality in Pregnant Diabetics. Strict Control of Diabetes with Conservative Obstetric Management. J. Pederson and E. Brandshup. *Lancet* 1: 607, 1956.

Since 1946 in Denmark, as many pregnant diabetics as could be collected from the whole country were treated before delivery at a Copenhagen hospital. There have been 265 cases in 10 years.

Ideally, the patient was kept in hospital from the thirty-second week of pregnancy, which was induced at about 37 weeks. During her stay, the diabetes was subjected to the strictest possible chemical control with a diet of about 1900 calories and liberal insulin. The method is described in detail. Ten per cent of the patients were seen relatively late in pregnancy and received an average of only 15 days treatment, compared to the rest who had an average of 45 days treatment.

In the cases with the longer treatment fetal mortality was only 10 per cent compared to 33 per cent in the rest and 38 per cent in diabetics before 1946. It is considered that these excellent results are due to the intensive medical care, rather than to any obstetrical methods—sex hormone treatment was not given and only 15 per cent were Caesarean sections. The infants were more nearly normal than the characteristic "diabetic" baby. The authors believe that the lowest fetal mortality achievable at present is about 6 per cent.—F. E. HYTTEN

Observations on Forty Babies of Diabetic Mothers 1948–1954. H. Medovy and G. H. Holman. *A.M.A. Am. J. Dis. Child.* 90: 606, 1955. (Soc. Trans.)

This is a review of 40 infants of diabetic mothers delivered at the Maternity Pavilion, Winnipeg General Hospital, 1948–1954. It includes all such infants delivered in the hospital during this period. There were four neonatal deaths, all associated with hyaline-membrane formation. In addition, 13 infants who survived had respiratory distress of varying degree. Thus, a total of 17 out of 40 infants manifested respiratory distress. This fits in with the experience of others who have pointed out that the respiratory tract of an infant of a diabetic mother is peculiarly vulnerable to hyaline-membrane formation. Investigation of this relationship is important as a possible means of solving the mystery of this condition. Convulsions occurred in two infants in the nursery period. These were associated with normal blood sugars but low serum calcium. Tremors and excessive irritability were observed in a few infants, but it was not possible to relate these signs definitely to the presence of low blood sugar. Serial electrolyte study on three infants failed to disclose any significant deviation from normal. The authors have so far not been able to confirm the presence of an Addisonian crisis in any infant of a diabetic mother, as suggested by Gauchat.

Delivery at term (14 cases, no neonatal deaths) is desirable wherever possible, and the dogmatic acceptance of "routine" delivery at 36 weeks' gestation and of "routine" Caesarean section is to be deplored. The added risk of hyaline-membrane formation in the latter groups must be considered before these procedures are attempted. There was no correlation between the duration of diabetes in the mother and the outcome of pregnancy. The occurrence of previous fetal death, even when repeated, apparently did not prevent some mothers from finally producing a normal living infant. The analogy to similar pregnancy histories among mothers with Rh incompatibility is noted. —AUTHORS

Parity and the Incidence of Diabetes. D. A. Pyke. *Lancet* 1: 818, 1956.

A statistical analysis of 953 diabetics attending the Radcliffe Infirmary, Oxford, is presented. There was an approximately equal sex incidence under the age of 45, but after that age there was a preponderance of women diabetics. The excess is "confined to women who have borne children and rises with increasing parity." A woman who has had five children appears to have about three times as great a chance of developing diabetes as a woman who has none, but childbearing does not lead to the earlier appearance of diabetes. The effect of parity was shown not to be due to obesity in the multiparae and it is considered that the menopause is also unlikely to be influential.—F. E. HYTTEN

The following excellent contribution should be carefully studied in the original by physicians engaged in the care of diabetic patients.

Aetiology and Management of Lesions of the Feet in Diabetes. W. Oakley, R. C. F. Catterall, and M. M. Martin. *Brit. M. J.* 2: 953, 1956.

Symptoms and signs of occlusive peripheral vascular disease in the lower extremities were found in 146 of 3788 diabetics attending King's College Hospital, London. There were no cases under the age of 40 and only nine under 60 years of age. The condition was more than twice as frequent in male diabetics as in females; there was no obvious relationship with either the duration or the severity of the diabetes.

It is considered that diabetic neuropathy, a degenerative condition particularly of lower extremity peripheral nerves, superimposed on arterial disease is the most important factor in the production of localized ulceration and gangrene. Pure ischemic disease also occurs but the high incidence of "so called vascular lesions" of the feet of diabetic patients is not in itself evidence of peripheral occlusive vascular disease.

The diagnosis and treatment of these conditions are described in detail. In particular a method of protecting the heels of bedridden patients is described and illustrated.—F. E. HYTTEN

METABOLISM OF AMINO ACIDS

The current concept of protein synthesis involves the organization of amino acids in ribonucleic acids located in microsomes and mitochrondria, the particles in which the principal oxidative enzymes are distributed. Further observations upon the mechanisms of protein synthesis by use of radioactive amino acids localizing the fabricating processes and the necessary accessory factors are eagerly awaited. The essential role of desoxyribonucleic acid (DNA) in protein synthesis has been established. It is of interest that Waterlow has reported that RNA in relation to DNA is low in the malnourished liver and rises on treatment.

Nucleic Acids and Protein Synthesis in Animal Tissues. A. Brigitte, J. L. Askonas, and T. S. Work. *Biochem. J.* 62: 40P, 1956.

Evidence that ribonucleic acid (RNA) is associated with synthesis of protein is presented. In animals injected with radioactive amino acids it was found that protein of the microsome fraction became labeled more rapidly than other cell proteins and that maximum labeling occurred in the ribonucleoprotein fractions of the microsomes.

In experiments using tissue slices or homogenates, maximal activity after incubation with radioactive amino acids has been found in the nucleo-protein fractions. The incorporation process is dependent on the presence of energy sources and on undegraded RNA in microsomes or DNA in nuclei.—M. K. HORWITT

Nucleic Acids and the Incorporation of Amino Acids. E. F. Gale. *Biochem. J.* 62: 40P, 1956.

Incorporation in fragmented bacterial or mammalian cell preparations requires a source of energy which can be supplied by ATP. In disrupted staphylococcal cells, incorporation of glycine or glutamic acid is inhibited by dinitrophenol, penicillin, bacitracin, chloramphenicol or 8-hydroxyquinoline. Removal of nucleic acid results in a decrease in the rate and amount of incorporation that will take place. Incorporation can be restored by addition of staphylococcal cells to the incubation mixture; DNA gives complete restoration whereas RNA is less effective. Treatment with deoxyribonuclease activity decreases the activity of DNA, while ribonuclease digestion of RNA results in decreased activity.

Fractionation of such RNA digests has resulted in separation of activating substances from the polynucleotide fractions and these substances appear to be non-nucleotide in nature. A "Glycine-Incorporation Factor" has been isolated.—M. K. HORWITT

The formation of large quantities of digestive protein enzyme factors by the pancreas suggests the need for an adequate dietary protein intake for maintenance of pancreatic exocrine function. The search for specific amino acids involved in the synthesis of these enzymes is of considerable interest.

Changes in Pancreatic Enzymes Brought About by Amino Acid Additions to the Diet. D. F. Magee and S. S. Hong. *Am. J. Physiol.* 184: 449, 1956.

Rats fed 7 per cent casein as the sole source of protein were divided into eight groups. Two of these were controls receiving an extra 1 per cent casein. The remaining groups were fed equal amounts of a diet containing 1 per cent of the following *dl* amino acids; isoleucine, methionine, phenylalanine, leucine, lysine or tryptophan. At the end of three weeks of feeding all of the animals were subjected to a 24-hour fast, then killed, and the enzyme activities in the pancreases were determined. It was found, by comparison with the controls, that no amino acid supplement increased amylase. Methionine increased lipase and protease activity and phenylalanine and isoleucine increased protease activity alone.—AUTHORS

In a recent note by Mirsky, the ingestion of tryptophan was stated to have a hypoglycemic effect. Several years ago, a similar action was attributed to the amino acid, glycine. These observations have not been satisfactorily explained although inhibition of insulinase has been suggested as the mode of action of tryptophan.

Familial Hypoglycemia Precipitated by Amino Acids. W. A. Cochrane, W. W. Payne, M. J. Simpkiss, and L. I. Woolf. *J. Clin. Investigation* 35: 411, 1956.

This is an interesting account of three cases of hypoglycemia occurring in one family and one unrelated case in which convulsions and profound hypoglycemia were induced by the administration of proteins or amino acids. In these subjects the glucose tolerance test was normal. Casein, leucine, or isovaleric acid causes a

marked fall in fasting true blood sugar level. Normal subjects do not show this response. It is postulated that leucine (or its metabolite isovaleric acid) may either enhance the effect of circulating insulin or stimulate insulin secretion.

In this type of "idiopathic" hypoglycemia small amounts of carbohydrate should be given 30 to 40 minutes after ingestion of a protein meal to offset the blood sugar lowering effect. This unexpected observation deserves further study.—S. O. WAIFE

Effect of Amino Acid and Glucose Ingestion on Arteriovenous Blood Sugar and Appetite. S. M. Mellinkoff, M. Frankland and M. Greipel. *J. Appl. Physiol.* 9: 85, 1956.

After normal individuals ingested an amino acid mixture, the blood amino acid concentration and the arteriovenous blood sugar difference increased. However, venous blood sugar was lower and appetite decreased. When glucose was taken by mouth appetite was observed to have an inverse relation with arteriovenous blood sugar difference. Appetite and serum amino acid concentrations were unrelated.—M. J. OPPENHEIMER

The metabolism of tryptophan is of particular importance in nutritional studies because of its role as a precursor in the endogenous formation of niacin. The excretion rates of the intermediary metabolites of this amino acid have been measured as a means of determining pyridoxine activity in several reports. While the determination of urinary levels of these metabolites is shown to account for a small percentage of ingested tryptophan, there is a high metabolic turnover rate as shown by the formation of CO_2 from the labeled amino acid.

Quantitative Studies on the Urinary Excretion of Tryptophan Metabolites by Humans Ingesting a Constant Diet. J. M. Price, R. R. Brown and M. E. Ellis. *J. Nutrition* 60: 323, 1956.

The studies of Heidelberger and associates demonstrated that tryptophan is a metabolic precursor of nicotinic acid in the rat. It has also been shown that the excretion of metabolites of nicotinic acid increases after the ingestion of tryptophan by man. In an effort to learn more about the metabolic fate of dietary tryptophan, studies have been done on human subjects ingesting a constant amount of tryptophan and nicotinic acid. The use of a constant diet has also made it possible to determine the daily variation in excretion of the major known metabolites of tryptophan and to determine the relative importance of nicotinic acid and these other metabolites. In addition, the effect of a single oral dose of 2.0 of l-tryptophan on the excretion of these metabolites was determined. These results have been compared with similar studies on subjects ingesting self-selected diets.

The urinary excretion of N-methyl-2-pyridone-5-carboxamide (pyridone), kynurenic acid, xanthurenic acid, kynurenine, N^8-acetylkynurenine, o-aminohippuric acid, anthranilic acid glucuronide and an unknown diazotizable aromatic amine was determined on four normal males ingesting a constant diet containing an estimated 15 mg of nicotinic acid and 900 mg of tryptophan. After six days on the constant diet 2.0 g of l-tryptophan was given as a single oral dose and the excretion of the metabolites was determined for six more days.

On the constant diet about 16 mg of pyridone were excreted per day. The other metabolites of tryptophan accounted for 2.5 per cent of the amino acid. Following the ingestion of a single 2.0 g supplement of tryptophan the pyridone excretion increased to an extent which would account for about 0.8 per cent of the dose. The increases in the excretion of the other metabolites account for 1.3 per cent of the supplemental tryptophan. Kynurenic acid, o-aminohippuric acid, and kynurenine were important urinary metabolites of the oral supplement of amino acid. Xanthurenic acid, acetylkynurenine and anthranilic acid glucuronide were minor metabolites by comparison.

A comparison of these results with data of a similar nature obtained with human subjects on a self-selected diet suggested that a constant diet was not necessary for quantitative studies on the metabolism of supplemental doses of tryptophan, unless the conversion to nicotinic acid and its metabolites was of particular interest.—B. SURE

Comparison of the Metabolism of Uniformly^{14}C-labeled L-Phenylalanine, L-Tyrosine and L-Tryptophan in the Rat. C. E. Dalgleish and H. Tabechian. *Biochem. J.* 62: 625, 1956.

Adult rats starved for 16 hours were given solutions of labeled amino acids by stomach tube in amounts (less than 1 mg) considered sufficiently small to approximate physiologic conditions. The radioactivity in respired CO_2 and in different organs was determined at varying intervals.

The rate of liberation of the label in the respired CO_2 showed that all three amino acids can be rapidly converted into non-aromatic substances of high metabolic activity. The rates of degradation of phenylalanine and tryptophan were similar and about one-half that of tyrosine. Hydroxylation to tyrosine is the rate-limiting step in normal phenylalanine metabolism.

The rate of appearance of activity in whole muscle, liver and gut and in the "protein-bound" and "non-protein bound aromatic" fractions of these organs, is reported. The specific activity of liver and gut protein exceeded that of blood protein whenever examined, but muscle protein was less active.

At present, no metabolic pathway is known to account for the comparatively rapid degradation of tryptophan. It was suggested that unless a major pathway of tryptophan metabolism remains undiscovered, degradation is most likely to occur via 3-hydroxyanthranilic acid which gives rise not only to nicotinic acid and quinolinic acid, but also to non-

nitrogenous substances with a high metabolic-turnover rate. Initial stages in the formation of such substances are proposed.—M. K. HORWITT

The dynamic equilibrium concept of tissue and plasma amino-acid pools receives further support. It is likely that identical amino acids can be individually exchanged within the molecular structure of protein.

Amino-Acids in Hepatic Venous and Arterial Blood. Investigated by Paper Chromatography. K. H. Onen, O. L. Wade and J. D. Blainey. *Lancet* 2: 1075, 1956.

Blood samples from the hepatic vein and brachial artery were taken simultaneously in ten subjects who were undergoing cardiac catheterization for the investigation of cardiac disease. None had disturbance of liver function. Catheterization was done seven hours after the last meal.

The total amino-acid content of hepatic venous blood was about half that of the arterial blood in all subjects. In most the levels of alanine, methionine, valine, leucine, isoleucine, cysteic acid glutamine and glycine were lower in the hepatic venous blood than in the arterial blood. The difference varied and was greatest in the case of alanine. In four subjects the glutamic acid was higher in the hepatic venous and in two it was the same as the arterial blood.

The constancy of the amino-acid level in the peripheral blood at rest, despite removal from the blood by the liver suggests the liberation of free amino-acids from the tissues into the circulation.—F. E. HYTTEN

Variation of Amino Acids in Human Blood Serum. H. Ven Horst, V. Jurkovich and Y. Carstens. *Amer. J. Clin. Path.* 26: 604, 1956.

One hundred specimens of human blood serum were studied by means of chromatograms. Variations were found in the composition of as many as 17 different amino acids. The variations were distinctly greater in sera obtained from hospitalized patients than from blood donors.—M. SILBERBERG

Effect of Fasting on Blood Non-Protein Amino Acids in Humans. L. W. Charkey, A. D. Kano and D. F. Hougham. *J. Nutrition* 55: 469, 1955.

Six adult human volunteers (five men, one woman) in good health, ranging in age from 22 to 42 years, served as experimental subjects. Blood levels and urinary excretion of specific amino acids before, during, and after a 48-hour fast constituted the principal experimental measurements made. Fasting in these adult humans led in 48 hours to increased blood levels of leucine and valine. Blood levels of five other amino acids, namely lysine, threonine, methionine, arginine and tryptophan, were simultaneously *reduced* by fasting. The response of adult humans to fasting, in terms of blood non-protein amino acid levels, was entirely different from that found in chicks up to six weeks of age, in that the blood levels of different amino acids were increased as a result of fasting. Examination of the literature revealed a correspondence, for the human species, between amino acids exhibiting a blood level rise during fasting and those not metabolically available by tissue conversion of structural analogues. A similar relationship had been found earlier in chicks. Hence it is suggested that a correspondence, between amino acids exhibiting increased blood levels due to fasting and those metabolically unavailable by precursor amination, may hold true for a variety of species.—B. SURE

There have been many methods proposed for determining the biologic value of protein. The practical application of in vitro *digestion of protein by proteolytic enzymes derived from the digestive tract for determining the availability of amino acids and protein utilization appears to be a fruitful approach to the problem.*

The Pepsin-Digest Residue (PDR) Amino Acid Index of Net Protein Utilization. A. L. Sheffner, G. A. Eckfeldt and H. Spector. *J. Nutrition* 60: 105, 1956.

Although the nutritional quality of a protein must, in the final analysis, be established biologically, there are many advantages to be derived from an *in vitro* method which accurately predicts the biologic value of a protein from its chemical composition.

The relationship between the pattern of amino acids released by digestive enzymes and the biologic value of food proteins was studied. The pattern of amino acids released *in vitro* by pepsin revealed differences between proteins which were not apparent from their total essential amino acid content nor from the patterns existing when the pepsin digests were further digested with trypsin and erepsin.

An amino acid index is described which takes into account the physiologic availability of amino acids during digestion. The new index combines the pattern of essential amino acids released by *in vitro* pepsin digestion with the amino acid pattern of the remainder of the protein to produce an integrated index—the Pepsin-Digest-Residue (PDR) amino acid index. The PDR index was closely correlated with the net protein utilization value of a variety of proteins. Division of the PDR index by the digestibility coefficient of the respective proteins yielded values which accurately predicted the biologic values of the proteins studied.—B. SURE

Renal tubular resorption of amino acids is presumably dependent upon transport mechanisms within the proximal tubular epithelium. These resorptive pathways are affected in various disease states such as hepatolenticular degeneration, nephritis, cystinosis, rickets and others. Further study of the actual mechanisms involved in this important aspect of amino acid metabolism is needed.

The Renal Tubular Response to Amino Acid Loading. P. D. Doolan, H. A. Harper, M. E. Hutchin and E. L. Alpen. *J. Clin. Investigation* 35: 888, 1956.

In three normal subjects the renal tubular reabsorption of parenterally administered amino acids was studied. Previous observations have indicated that when the load of amino acids to be filtered by the kidney was increased, the amount of amino acids reabsorbed and excreted was also increased. Most noteworthy was the increase in the amount reabsorbed, and considerable selectivity was exhibited in the matter of reabsorption of individual amino acids. In the present study the solution of amino acids used for loading was administered at a faster rate than in previous experiments and was further supplemented with additional glycine. The results indicate that striking differences in rates of reabsorption exist among individual amino acids, and this may be explained by assuming that they are handled by independent mechanisms or by the same mechanism at different rates. Glycine, serine and threonine were reabsorbed in amounts no greater when the load was high than when the load was low; whereas, other amino acids—including alanine, lysine, phenylalanine, tryptophan and valine—were reabsorbed at an increasing rate as the filtered loads were elevated. Glycine, when infused alone, was more completely reabsorbed than when included in the amino acid mixture. An interesting observation was that the infusion of glycine alone was accompanied by an increase in the excretion of two amino acids, serine and threonine; and there were data suggesting that toxic effects from glycine infusion may have been due to ammonia intoxication. Although competition in absorption undoubtedly exists, the authors present evidence for the suggestion that the reabsorptive capacities for some amino acids take place independently of competitive shifts. This decrease may represent a so-called fatiguing of the reabsorptive mechanisms due to an excessive concentration of either an antimetabolite, a reaction product, or perhaps a toxic phenomenon.—S. O. WAIFE

GASTROINTESTINAL PHYSIOLOGY AND NUTRITION

The regulation of food intake is a complex mechanism involving certain hypothalamic centers which control sensations of hunger or satiety. The activity of these centers are in part responsible for changes in gastric motility and secretion. Precise localization of the hypothalamic nuclei constituting the feeding centers has been achieved by means of stereotoxic experiments which have demonstrated areas both stimulatory and inhibitory upon appetite and gastric activity. It is suggested in the following works that anorexogenic agents and vitamin deficiency may operate through activation of inhibitory centers.

A Study of the Electrical Activity of the Hypothalamic Feeding Mechanism. J. R. Brobeck, S. Larson, and E. Reyes. *J. Physiol.* 132: 358, 1956.

In this study the test objects were cats which had been anesthetized with pentobarbital sodium or a mixture of dial-urethane. Electrical activity was recorded from the hypothalamus and adjacent diencephalon. Congeners of amphetamine produced alterations in electrical activity, which was recorded from the medial hypothalamus. This may represent stimulation of the ventromedian hypothalamus, which has been postulated to contain the inhibitory part of a feeding center. These nuclei then inhibit in turn the lateral hypothalamus in which the more basic mechanism for food intake is localized. The depressing action of amphetamine on food intake could thus be explained, although other possibilities are not ruled out.—M. J. OPPENHEIMER

Mechanism of Anorexia in Vitamin-Deficient Hyperphagic Animals. L. R. C. Agnew and J. Mayer. *Nature* 177: 1235, 1956.

In the rat and mouse, ventromedial hypothalamic nuclei act as "satiety brakes" which, in response to stimuli, (particularly metabolic) inhibit a constantly activated feeding mechanism, apparently initiated at the level of the anterolateral nuclei. Destruction of the ventromedial nuclei does not increase hunger, but shortens the pauses between feeds. The centers can be injured by administering gold thioglucose. Experiments are reported which show the value of animals so treated in an analysis of the mechanism of anorexia. It was shown in one that thiamine deficiency immediately eliminated the hyperphagic tendency of the thioglucose-treated animals, presumably through direct inactivation of the "feeding" mechanism. In vitamin A deficiency there is no such inhibition; thioglucose-treated rats who were vitamin A-deficient, were markedly hyperphagic.—F. E. HYTTEN

Inhibition of gastro-intestinal motility can be produced by local mechanisms which are dependent upon the types of feeding employed, such as high-fat intake or by variations in the osmotic properties of the lumenal contents.

Some Properties of an Alimentary Osmoreceptor Mechanism. J. N. Hunt. *J. Physiol.* 132: 267, 1956.

In order to study gastric emptying in human patients, test meals of 750 ml were administered. The volume of gastric contents was then determined at intervals. Phenol red was used as a marker for the test meals. In itself it did not influence emptying time. When bland meals were introduced into the stomach via a tube, the stomach emptied more rapidly than when similar meals were taken by mouth in the usual fashion. Stomach emptying after test meals of water were delayed by sucrose in a concentration of 35 grams per liter. With up to one hundred milliequivalents per liter of NaCl, either swallowed or by stomach tube, the rate of emptying of test meals was increased. From 160 to 350 meq/l NaCl slowed emptying. Ten meq HCl/l in test meals delayed gastric emptying if it came in contact with "precardial" receptors. If the same test meal was kept from contact with these receptors, there was no change in the time required for the stomach to empty. Potassium chloride or glucose via

stomach tube inhibit emptying as concentrations increase. Sodium bicarbonate or chloride and urea produced biphasic results as concentrations were raised; emptying time was decreased at lower but increased at higher concentrations. Sorbitol, with one exception, slowed gastric emptying as concentrations increased. A single type of receptor is postulated which slows gastric emptying. These osmoreceptors are stimulated by the work done by the mechanism which separated a fixed volume of constant osmotic concentration from the contents of the lumen. Emptying is fastest when these receptors are least stimulated.—M. J. OPPENHEIMER

Methods for studying the intestinal absorption rates of the products of digestion have been difficult to evaluate. In glucose and amino acid absorption studies, the liver is interposed between the systemic venous blood obtained for analysis and the sites of absorption. Since a large ratio of absorbed fatty acids may reach the systemic blood through the thoracic duct rather than through the portal system the use of I^{131}-labeled fat may provide an accurate index of fat absorption.

I^{131}-labeled Fat in the Study of Intestinal Absorption. J. M. Ruffin, W. W. Shingleton, G. J. Baylin, J. C. Hymans, J. K. Isley, A. P. Sanders and M. F. Sohmer, Jr. *New England J. Med.* 255: 594, 1956.

A large number of patients with a variety of disorders of the gastrointestinal tract were fed I^{131}-labeled fat. Absorption of the radioactive fat was followed by determining the radioactivity of the blood at hourly intervals for six hours following ingestion of the fat. Fecal excretion of the radioactive fat was followed for 48 hours after the feeding. An inverse relationship was found between fecal excretion and the amount of radioactive fat found in the blood which indicated that either could be used to measure the amount of I^{131}-labeled fat absorbed.

Patients with the following clinical conditions: relapsing pancreatitis, sprue, Whipple's disease, carcinoma of the pancreas, also, patients who had had an operation for peptic ulcers showed decreased absorption of the radioactive fat. In the group of cases diagnosed as functional gastrointestinal disturbances, the blood levels and fecal excretion of the I^{131}-labeled fat were within normal limits.

The authors suggest that, since this is a simple and accurate method of determining fat absorption, it could be used in the clinical diagnosis of conditions in which there is abnormal fat absorption.—M. W. BATES

Small intestinal diverticulae have usually been considered to be insignificant and incidental findings. Exceptions to this concept are found in those cases where diverticulae may involve the duodenum at the level of the ampulla of Vater producing obstruction or in cases such as the following.

Diverticulosis of the Small Intestine with Steatorrhea and Megaloblastic Anemia. D. D. Gellman. *Lancet* 2: 873, 1956.

A case is described of a woman 60 years of age who was first seen primarily because of dyspepsia. The only obvious finding was a hiatus hernia and she improved with minimal treatment. She was next seen a year later "almost moribund." She had lost considerable weight, had diarrhea and vomiting, and her hemoglobin level was 6 g/100 ml. After immediate treatment she was re-examined and a barium meal revealed numerous diverticula in the jejunum and upper ileum. In retrospect the diverticula appeared to have been present at the x-ray examination a year previously.

She absorbed 87 per cent of fat in a diet containing 82 g. Her absorption of vitamin B_{12} was poor but this became normal after a course of chlortetracycline.

It is considered that stagnation and bacterial growth occur in the diverticula and that the bacteria destroy or compete for the antimegaloblastic substances.—F. E. HYTTEN

Intestinal Obstruction by Food. J. T. Rowling. *Lancet* 2: 289, 1956.

Two cases are reported of complete intestinal obstruction due to undigested masses of orange. They were a man 63 years of age and a woman 60 years of age. In both the symptoms were severe. Both had had partial gastrectomies. Although there have been many reports of obstruction due to a variety of food masses, this has rarely been reported in patients with partial gastrectomies. It is suggested that the intermittent attacks of pain often seen in persons following the operation may be due to colic associated with undigested food masses.—F. E. HYTTEN

A Short Small Intestine Associated with Fibrosis of the Liver. C. Raeburn and A. J. Brafield. *Lancet* 1: 884, 1956.

Five cases are described in which severe hepatic fibrosis was associated with a small intestine of much below average length. The lengths ranged from only $4^1/_2$ feet to 14 feet and appeared to be due to hypoplasia rather than to disease. It is suggested that the liver disease may have followed chronic malnutrition due to the small intestinal absorptive surface.—F. E. HYTTEN

Nutritional care in patients with surgical complications of the gastrointestinal tract requires expert planning and continuous supervision. It is of primary importance to provide an adequate caloric intake by whatever means available to promote the sparing of protein for tissue repair.

Nutritional Management in Duodenal Fistula. D. W. Smith and R. M. Lee. *Surg. Gynec. & Obst.* 103: 666, 1956.

The authors review briefly some of the factors important in the occurrence and therapy of duodenal

fistula. Their central thesis is: "malnutrition is the greatest pre-existing cause of postoperative duodenal fistulas" and "patients with profuse drainage of duodenal contents and loss of much of their oral intake have a severe negative nitrogen balance and develop a rapid loss of body proteins, which is the major factor in the extremely high mortality associated with duodenal fistula." Accordingly, they outline, first, a regimen for the preoperative repletion of nutritionally depleted patients who are to undergo upper gastrointestinal tract surgery (and therefore subject to duodenal fistula as a postoperative complication) and, second, a regimen for the therapeutic care of patients with established duodenal fistulas. They place their chief reliance on continuous 24-hour drip tube feedings given intragastrically to those without duodenal fistulas and given intrajejunally by a fine plastic nasojejunal tube to those with duodenal fistulas.

A method for nasojejunal intubation in gastrectomized patients is described. The tube-feeding mixture "contains 65 grams of protein, consisting of partially hydrolyzed lactalbumin, and 160 grams of dextrose per lit with all necessary electrolytes and trace minerals. The formula provides 900 cal per liter of solution. Alcohol may be added for sedation or for additional calories, providing approximately 350 cal per 50 cc. Vitamins are supplemented by addition to the feeding solution or by injection. During the first 24 hours of tube feeding only 1 lit is administered by carefully controlled constant drip of about 10 to 15 drops per min. This amount is gradually increased, by not more than 500 cc daily, to $1\frac{1}{2}$ or 2 liters or more daily. . . . ." The usual methods were employed in the local treatment of the fistula tract, including continuous suction sump drainage. Antibiotics were administered also; in a few patients Banthine was given. Eleven patients with duodenal fistulas were successfully treated—an impressive record.—S. M. LEVENSON

Gastroenteritis produces an inflammatory change in the intestinal mucosa which produces enhanced permeability. This permits the absorption of proteins and sugars in an unhydrolyzed state. Sucrosuria is a consequence of this condition in certain instances; other causes of this disorder are described.

Sucrosuria in Children. J. A. Owen and I. C. Lewis. *Scot. Med. J.* 1: 231, 1956.

Six infants who passed sucrose in their urine are described. They were from one week to nine months of age and five of them were under treatment for gastroenteritis.

On the basis of these cases and from others described in the literature, the authors believe that three types of sucrosuria exist. The first type is that with some gastrointestinal disturbance, such as gastroenteritis, which allows more than the normal trace to be absorbed. The second type is apparently able to synthesize sucrose in the body. In the third type sucrosuria is presumed to be "alimentary in nature," that is, a certain amount is normally absorbed from a large amount ingested.—F. E. HYTTEN

The successful treatment of peptic ulcer requires neutralization or suppression of the excessive hydrogen ion secretion by the gastric mucosa. Diet has been considered an essential aspect of ulcer therapy to avoid the chemical and mechanical irritants which stimulate secretion. The use of a free diet recommended below will require careful and well-controlled evaluation.

Treatment of Peptic Ulcer in the Aged with Unrestricted Diet. E. A. Marshall and M. Sass. *J. Am. Geriatrics Soc.* 4: 498, 1956.

The authors present their studies on the treatment of 292 cases of peptic ulcer in patients over 60 years of age, using an unrestricted diet. They combine this with rather conventional antiacid, antispasmodic and sedative therapy. A method of administering the drugs which attempts to maintain low acid peptic activity is carefully described. They also feel that most patients can be started on a diet of their choice within 24 hours after initiating the antacid regimen. This also includes non-stenotic obstruction and hemorrhage. The failure rate of their method while the patient was under observation was only 5.5 per cent.

The long term results are somewhat difficult to evaluate in view of the inadequate follow up. Forty-four per cent of the patients were the last to be followed up. The patients known to have a good result constituted only 40 per cent of the original series.—K. R. CRISPELL

Effect of Polyaminostyrene on Gastric Acidity. B. H. Bass. *Brit. M. J.* 1: 1406, 1956.

Polyaminostyrene is an anionic exchange resin. It is converted into the chloride by gastric HCl, thus neutralizing the gastric acidity, and then returns to its original form in the alkaline medium of the small intestine. The unchanged resin is excreted in the feces.

The resin constitutes an almost perfect antacid. Since it forms no gas in the stomach, there is no electrolyte loss from the body, and no risk of alkalosis.

Its effect was tested on five ulcer patients who had a high gastric acidity, with entirely satisfactory results. Free acid disappeared from the stomach within an hour of taking the tablets, and three of the patients reported relief of pain within ten minutes.—F. E. HYTTEN

Influence du Vinaigre sur le Transit Gastrojejunal Apres Gastrectomie Subtotale. C. Auguste, F. Guerin and G. Toison. *Arch. d. Mal. de l'App. Digestiv. et Malad. Nutrition* 44: 119, 1955.

The authors present their study of the action of vinegar on gastrojejunal motility after a subtotal gastrectomy. One of the consequences of achlorhydria in gastrectomized patients is the elevation of the pH in

the first jejunal loop. This acidification will retard gastric evacuation, as has been demonstrated by others. The authors have utilized for their study a meal composed of barium to which was added chopped meat, margarine and mashed potatoes. Fifteen patients with subtotal gastrectomies received this meal. The time of evacuation of the stomach is determined by x-ray.

After many hours, the same patients received the same barium meal with 40 ml to 60 ml of diluted vinegar in water at pH 2. X-rays showed that vinegar induced a spasm of the efferent intestinal loop which will retard the evacuation of the stomach. In both experiments, there was no significant difference in the time during which the meal reaches the caecum. (The significance of this study is that an acid inhibits the sudden evacuation of the stomach, which produces quick distention of the jejunum and very often causes a dumping syndrome.)—J. JACOBSON

Effect of Antrum Exclusion on Gastric Secretion. W. R. Waddell. *J. Appl. Physiol.* 9: 222, 1956.

This investigation is based upon a comparison of acid secretory tests carried out on patients in a control period before operation and later repeated after vagotomy and antrum exclusion for duodenal ulcer. A further evaluation considering vagotomy and antrum exclusion as against vagotomy and gastroenterostomy is included. In this manner it has been possible to assign a role to the intrinsic innervation of the stomach in its relation to acid secretion. When the stomach had been transected a decrease in basal acid output was observed. This same operation was followed by a diminished response to histamine and insulin stimulation. The author concluded that the intrinsic postganglionic parasympathetic innervation has been interrupted. These fibers pass from the antrum to the parietal cells in the gastric mucosa.—M. J. OPPENHEIMER

NUTRITIONAL ASPECTS OF ATHEROSCLEROSIS

Atherosclerosis represents the result of two processes; the first is an alteration of the vessel wall with deposition of mucopolysaccharide material and the second is an infiltration of the disturbed vascular areas with lipid material. These two processes are affected by aging, sex, dietary, and genetic factors. Other conditioning factors include the level of physical activity and the presence of certain diseases such as diabetes, myxedema, and nephrosis.

Aging and Atherosclerosis. Transcription of a Panel Meeting. H. S. Simms, F. E. Kendall, A. Kellner, and J. M. Steele. *Bull. New York Acad. Med.* 32: 517, 1956.

Atherosclerosis is a disease which is present in all ages to some degree, but since it is accumulative in effect, clinical manifestation of the disease is usually found more in older people.

Atherosclerosis should be considered a metabolic disease involving faulty or abnormal metabolism of all lipids rather than of cholesterol alone. It is believed by some to be manifested by increase in β-lipoprotein levels in human beings. Much evidence indicates that the β-lipoprotein plays a more specific role than serum cholesterol in the development of atherosclerosis. The basic metabolic lesion that leads to the elevated β-lipoprotein may lie in the inability of peripheral cells to take up and utilize lipids which are supplied to them in plasma. It has been shown that an injection of heparin increases an individual's ability to clear lipid from the blood stream. The clearing factor is a lipase which is released from the cells following an injection of heparin. Patients with severe atherosclerosis produce less clearing factor in their blood following the injection of heparin.

Hormonal imbalances will produce marked changes in serum lipid patterns. Estrogens and androgens produce shifts in α- and β-lipoprotein fractions. The estrogens shift cholesterol from β- to α-lipoprotein fractions. Androgens act in the oposite direction.

Atherosclerosis does not cause hypertension nor does hypertension cause atherosclerosis, though hypertension may have an important accelerating effect in the development of atherosclerosis. As blood pressure increases, more lipid may penetrate into the intima of the blood vessel.

There is no specific therapy for atherosclerosis. It is likely that diet plays a large role in the development of the disease. Cholesterol and probably other kinds of lipids in the diet may increase the rate of development of atherosclerosis. Eggs, which contain much cholesterol, have been implicated as a factor in causing high blood cholesterol levels, but a normal person has to consume great quantities of eggs before there is a slight increase in blood cholesterol level. It is possible that egg ingestion may have greater effects on blood cholesterol levels in persons with coronary atherosclerosis.

Many problems exist in this field. It is very useful to have such a clear presentation of the established facts and a definition of the difficulties that exist.—M. W. BATES

Many important links in the chain of evidence incriminating a high-fat intake as a primary cause of atherosclerosis have accumulated through the research of Keys and others. Specific recommendations for practical changes in our dietary habits are presented with appropriate justification for these suggestions on biochemical grounds. A considerable amount of research is required for full evaluation of the role of the unsaturated/saturated fatty-acid ratio in relation to atherogenesis.

Nutrition and Atherosclerosis. L. N. Katz, J. Stamler, and R. Pick. *Fed. Proc.* 15: 885, 1956.

In this provocative review of the interrelationships of nutrition and atherosclerosis, the Michael Reese group presents evidence that the diet which encourages the development of atherosclerosis and which is so typical

of modern-day America is characterized by an excessive intake of calories-cholesterol-lipids and by an inadequate intake of essential vitamins-minerals-amino acids-unsaturated fatty acids. The correction of this unfortunate tendency would seem to be quite feasible. In the authors' words, it involves the substitution of broiling meat for deep-fat frying and roasting, the abandonment of the habit of pouring gravies on meats and sauces and dressings on vegetables and salads, and substituting fresh or cooked fruit for such desserts as pie a la mode, pastries, etc. These changes, together with an increased consumption of fruits and vegetables and whole-grain products, would automatically cut down calories and, presumably, obesity, and raise the ratio of essential nutrients to calories; at the same time, it would reduce the per cent of total calories in the form of fat from the present 40 to 60 per cent to 25 to 30 per cent.—S. O. WAIFE

Dietary Aspects. F. J. Stare. *Fed. Proc.* 15: 900, 1956.

Dr. Stare makes the point that although there are relationships between the differences in fat intake and the incidence of atherosclerosis in various racial groups, many other differences in the diet (among them the type of fat and carbohydrate, the quantity and quality of protein, vitamin and mineral content, and amount and type of activity of the subjects) may be influencing cholesterol metabolism.

Furthermore, in data from the Department of Agriculture, it is found that during the twenty-year period from 1935 to 1955, the average caloric consumption per capita per day decreased by about 70 calories. Protein intake increased from 90 to 97 g and fat from 134 to 148 g, and carbohydrate consumption decreased from 440 to 384 g. The decreased use of potatoes and cereals with an increase in milk, meat, and eggs seemed to be responsible for these changes. Since the consumption of carbohydrates decreased, the percentage of fat in the diet would show an increase even if the total fat consumed had not changed.

The author throws some doubt on the statement that there has been an increase in fat consumption by Americans in recent years. It is true, however, that the use of hydrogenated fats has increased. The increased consumption of such hydrogenated fats does not necessarily mean a decrease in the intake of essential fatty acids, because there has also been an increase of these same oils in an unhydrogenated state. Furthermore, gross measurements of changes of saturation induced by hydrogenation do not indicate necessarily the degree of change in the content of biologically-active linoleic and linolenic acids. The author then concludes that a rational therapeutic approach would be available if we knew *how* the diets should be changed.—S. O. WAIFE

Age, Sex, Serum Lipids, and Coronary Atherosclerosis. D. Adlersberg, L. E. Schaefer, A. G. Steinberg, and C. I. Wang. *J. A. M. A.* 162: 619, 1956.

Individuals were selected at random from a healthy group of industrial workers and dependents of low-middle income in New York City in order to establish cholesterol and phospholipid levels appropriate for this population group. Approximately 1200 males and females between the ages of 2 and 77 years were examined. The overall observations indicate that the cholesterol and phospholipid levels for males remained constant through age 19, increased from age 20 to 33, and then remained constant to age 60. The levels for females were constant through age 32 but then increased sharply and continuously through age 58. The actual values of blood cholesterol for persons about age 60 were 236 mg for males and 263 mg per 100 ml for females as measured by the Sperry-Schonheimer method. The changes in serum phospholipid levels with age were similar to those found in blood cholesterol. Furthermore, the cholesterol-phospholipid (C/P) ratio appeared to be a function of the changes in serum cholesterol level and was independent of age. These data, although based on a specific population group, indicate that the period of marked increase in serum lipid levels which occurs "physiologically" in both sexes starts 13 years later in women than in men and lasts 12 years longer.

The reader will recognize that in these apparently "normal" individuals, a variable degree of atherosclerotic changes was already present. This is one of the major stumbling blocks in atherosclerosis research.—S. O. WAIFE

Not only does a high-fat diet lead to rises in serum beta-lipoprotein and cholesterol favoring atherogenesis but present evidence indicates that certain phospholipids included in such diets will promote blood coagulation.

Xanthomatosis and Atherosclerosis Produced by Diet in an Adult Rhesus Monkey. G. V. Mann and S. B. Andrus. *J. Lab. & Clin. Med.* 48: 533, 1956.

Perhaps one of the most controversial, yet important, issues of the day is the relationship between diet and atherosclerosis. Although the various attempts to relate mass population dietary data to various clinical manifestations or autopsy material is suggestive, the actual proof is lacking. For obvious reasons there has been no well-controlled, long term feeding experiment in humans. Whether or not it will ever be possible, is conjectural. In lieu of this, experiments involving the primate series would be next best.

In the course of such experiments the authors report their experience with one Rhesus monkey. The animal was five years old when the study began. It was fed a diet which contained 70 per cent fat and 6.51 g of cholesterol per 100 g of diet. After 1388 days on this diet, with slight modifications, as will be mentioned, the monkey was autopsied.

On this regimen the animal gained weight for 37 months and then began to lose weight. After 30 months nodules appeared on the surface of the palms and soles which were followed later by yellowish in-

filtrates in the skin, first over the appendages and later—other parts of the body. Toward the end of the experiment, emotional instability was noticed. However, at the time of sacrifice, the animal was still in good clinical condition.

The striking changes occurred in the serum beta-lipoproteins and cholesterol which rose precipitously following the institution of the diet, so that after three to four months, the serum cholesterol was 1200 mg/100 ml at which level it remained. The lipid phosphorus level rose proportionately. The rise in beta-lipoproteins involved the S_f O-35 particles so that the serum did not become lactescent.

The addition of 1000 mg of cysteine per day or the substitution of casein for soybean protein did not significantly alter the blood lipids, nor did the reduction in cholesterol from 6.51 g to 1.51 g/100 ml.

At autopsy the most striking features were the numerous large xanthomatosis deposits in the skin and tendons and the marked atherosclerosis of the large and median arteries, particularly the aorta and its branches. Involvement of the coronary arteries was extensive, although no myocardial abnormalities were found. A distinct centrifugal pattern of progression was noted. Ulceration and thrombosis of the endocardial surfaces were not seen. The intima and media were primarily involved. Although there were many similarities to human atherosclerosis, the prominent loss of medial musculature, the lack of intimal ulceration and thrombosis and the prominence of foam cells do represent deviations.

The evidence cited by these workers certainly adds more credence to the theory that high-fat, high-cholesterol diets are atherogenic and suggests further that diet is one, although not the only, factor important in human atherosclerosis. It is interesting that, here again, severe atherosclerosis can be produced in an animal, yet thrombotic manifestations do not occur. It would seem that emphasis should be placed not only on the etiology of the histologic vascular changes, but also on the effect of dietary on blood coagulation. Certainly the relation of feeding to occlusive vascular disease is unclear. Thus the battle rages!—J. F. MUELLER

Atherosclerosis. IV. The Relation of the Composition of the Blood Lipids to Atherosclerosis in Experimental Hyperlipemia. E. F. Hirsch and R. Nailor. *A.M.A. Arch. Path.* 61: 469, 1956.

Rabbits fed a diet enriched with cream and 1 per cent cholesterol rapidly developed hyperlipemia. The degree of hyperlipemia in cholesterol-fed rabbits considerably surpassed that observed in those fed cream only. All fractions of the blood lipids participated in the rise, the free cholesterols and cholesterol esters gradually exceeding that of all other fractions. Apparently, due to saturation of the blood with cholesterol, focal lipid deposits appear in the lining cells of the aorta and in the macrophages of liver, spleen, and other tissues. These focal deposits are thought to form, in susceptible arteries, the nucleus of atheromatous plaques developing subsequently.—M. SILBERBERG

Autopsy Correlation with Clinically Determined Atherogenic Index. I. Chapman, A. Goldbloom, G. Mirrer, and H. B. Eiber. *A.M.A. Arch. Pathol.* 61: 357, 1956.

In six patients 80 to 100 years of age, the atherogenic index determined according to the criteria established by Gofman was of the same order or below that found during the third decade. The aortae and coronaries of these patients were examined after death and all showed the lipoidosis type of arteriosclerosis. These findings seem to contradict the theory of a causal relationship between atherogenic index and atherosclerosis.—M. SILBERBERG

The production of coronary atherosclerosis together with renal lesions upon exposure of experimental animals to prolonged cold stimulus recalls the researches on stress by Selye. It is of interest that serum lipids were elevated in these animals and that choline added to the diet increased the incidence of arterial lesions. The effect of cold stress upon the histopathology of the vessels prior to lipid infiltration would be worthy of study.

Deposition of Fat in Coronary Arteries after Exposure to Cold. E. A. Sellers and R. W. You. *Brit. Med. J.* 1: 815, 1956.

When rats are exposed to a cold environment (1°–3° C) for long periods, many metabolic changes take place. They have been described in previous papers from this group and are thought to be adaptive.

In this study Wistar rats were kept at from 1°–3° C for from 10 to 18 months on a normal stock diet. More than half of them developed a lipoidosis of the coronary vessels, and in some there were aortic lesions. All had renal lesions, but they varied greatly in type and severity. The systolic blood pressure, measured directly, was not affected. Serum total lipids and free and bound cholesterol were significantly increased.

Coronary lipoidosis was produced in rats fed a high-fat, high-cholesterol diet with choline and exposed to cold for six weeks. Myocardial lesions were also observed in such "cold" rats whether choline was present or not. Arterial lesions were not observed in "cold" rats fed the same diet without choline.—F. E. HYTTEN

The fat intake is an important consideration in maintaining the caloric requirements. However, in certain parts of the world, the caloric demand is met by a high-carbohydrate allowance with a low intake of fats. There appears to be a homeostatic mechanism in the formation of endogenous fat so that acetate derived from carbohydrate can be rapidly converted to fat in the liver. Thus experimental animals receiving a high-fat intake converted less acetate into fat than those receiving a low-fat allowance.

The Effect of Fat Intake on Incorporation of Acetate-2-C^{14} into Liver Lipide and Expired Carbon Dioxide. E. G. Brice and R. Okey. *J. Biol. Chem.* 218: 107, 1956.

The effect of varying fat intake without altering the intake of calories and protein was studied in relation to excretion of $C^{14}O_2$ and synthesis of labeled liver lipides following single intraperitoneal injection of acetate-2-C^{14}. Weanling male rats were fed for three weeks prior to injection either (a) a diet containing 5 per cent fat and 18 per cent casein *ad libitum*, (b) a diet containing 40 per cent fat in amounts adjusted to match the calorie and protein intake of the first group, or (c) the 40 per cent fat diet *ad libitum*. Respiratory CO_2 was measured at frequent intervals for total CO_2 and $C^{14}O_2$ content. After the last CO_2 collection, the rat was decapitated, and the liver removed, weighed and divided into weighed aliquots.

The radioactivity of the fatty acids and the cholesterol of the livers were determined. Liver samples were saponified, diluted with water and extracted with petroleum ether. The label appeared promptly in the liver fat and cholesterol on both low and high fat diets. The fat content of the livers averaged 3.5, 6.9 and 8.9 per cent, respectively, for diets a, b and c.

The $C^{14}O_2$ expiration studies showed that the maximal specific activity of each rat was reached within $^1/_2$ to one hour after injection. During this period the rats fed the 40 per cent fat diet showed higher specific activities than those fed the 5 per cent diet. After one to two hours the specific activities of both groups were very similar. In all rats the incorporation of a large proportion of the injected C^{14} into $C^{14}O_2$ took place during the first hour. After three hours the rate of excretion was much lower and was more or less constant up to 24 hours. The lower rate of excretion is interpreted as due to oxidation, not of acetate but of compounds into which acetate-C^{14} has been incorporated. Total output of CO_2 was not notably affected by levels of fat fed nor by the slightly higher calorie intake of the *ad libitum* group.

The livers of both groups receiving the 40 per cent fat diet were significantly richer in fat than those of litter mates receiving the 5 per cent fat diet. The specific activity of liver fatty acids and the percentage incorporation of injected C^{14} into liver fatty acid was much greater in rats fed 5 per cent fat than in those fed 40 per cent fat. The data indicate that diets high in fat lowers the amount of liver fatty acid synthesized from acetate, but does not stop the process. The data for cholesterol were inconclusive.—M. K. Horwitt

CORTISONE AND NUTRITION

The adrenal steroids, cortisone and hydrocortisone, have been shown to enhance gluconeogenesis from amino acids. This action will elevate urea formation and increase the availability of glucose which is released from the phosphorylated intracellular phase by glucose-6-phosphatase. However, the action of these steroids which may be responsible for the alteration of the glucose tolerance test is probably that of inhibiting insulin activity. The failure of cortisone to affect the fructose tolerance test can be attributed to the intracellular shift of fructose which occurs without insulin.

The Effects of Cortisone on the Fructose and Glucose Tolerance Tests of Normal Men. *J. Lab. & Clin. Med.* 48: 13, 1956.

The effect of cortisone on the fructose and glucose tolerance tests of normal men is reported. The study confirms previous studies that cortisone does alter the glucose tolerance test. The cortisone effect was most striking in its prevention of the normal hypoglycemic phase of the response to the glucose load. Cortisone had no effect on the glucose tolerance curve in two of the ten subjects. Fructose tolerance was not influenced by the administration of cortisone. To explain these results the authors suggest that cortisone must act prior to the splitting of six carbon molecules into three carbon fragments in the glycolytic cycle.

The above studies are at variance with the studies of Frawley who administered a fructose load during a constant infusion of hydrocortisone. Frawley found elevation of blood fructose but no alteration of glucose tolerance when hydrocortisone was used. Further studies are needed to clarify this discrepancy. —K. R. Crispell

Aside from the effect of thiamine depletion upon carbohydrate metabolism in which hyperpyruvemia is seen, there are insufficient data available relative to the influence of other B-vitamin deficiencies upon this phase of metabolism. The action of cortisone as it alters carbohydrate metabolism may be a useful adjunct in clinical and laboratory investigations of vitamin-deficiency states.

Effect of Adrenal Hormones on Carbohydrate Metabolism in Riboflavin and Pantothenic Acid-Deficient Dogs. L. Arnrich, M. R. Nelson, M. R. Gram, and A. F. Morgan. *Am. J. Physiol.* 186: 427, 1956.

Fasting blood lactic acid levels rose 100 per cent in 11 to 13 weeks in riboflavin-deficient dogs as did in lesser degree blood pyruvic acid. Eosinopenia was marked also in this deficiency, but eosinophilia characterized late pantothenic acid deficiency. Swimming stress caused excessive rises in blood glucose and lactic acid in riboflavin-deficient but not in pantothenic acid-deficient and normal dogs. Marked eosinopenia was caused by swimming in the normal but not in any of the deficient animals. The normal and pantothenic acid-deficient dogs, following epinephrine treatment, showed the usual rise and fall in blood glucose and lactic acid, increased liver glycogen and marked eosinopenia. Cortisone treatment produced lowering of glucose and lactic acid blood levels in normal and riboflavin-deficient dogs but a rise in glucose in the pantothenic acid-deficient animals. Enlarged and hemorrhagic adrenals of lowered ascorbic acid content were usually found in the severely riboflavin-deficient dogs but

significantly fatty livers only in the animals which had succumbed in hypoglycemic collapse. The pantothenic acid-deficient dogs had adrenals of nearly normal composition in spite of hemorrhagic lesions and moderately fatty livers. The adrenal cholesterol was normal in both deficiencies. In riboflavin-deficiency in both stressed and unstressed conditions, dogs manifest some signs of hypoxia, hypersensitivity or over-production of epinephrine but no adrenal cortical failure. Pantothenic acid-deficient dogs show little evidence of hypoxia or epinephrine sensitivity but signs of hypocorticalism.—AUTHORS

The work of Grey and Shay has demonstrated an increase in the gastric phase of acid secretion following cortisone administration. The hypothalamo-pituitary-adrenal cortex circuit is involved in this reaction since interruption of this relay will lower this second rise in gastric acidity. The clinical counterparts of these observations are reported below.

Influence of the Adrenal Cortex on Gastric Secretion in Man. J. Kyle, J. S. Logan, D. W. Neill, and R. B. Welbourn. *Lancet* 1: 664, 1956.

Gastric secretion was studied in 11 patients with Cushing's syndrome, eight before and seven after subtotal adrenalectomy. In addition, the excretion of reducing corticoids and 17-hydroxycorticoids was measured in normal people and patients with various abnormalities of gastric secretion.

Gastric secretion, measured by the gruel fractional test-meal technic, was often increased in Cushing's syndrome and was restored to normal after adrenalectomy. The excretion of reducing corticoids is often high in hyperchlorhydric people with no other signs of endocrine dysfunction, and a high excretion of 17-hydroxycorticoids is usually accompanied by hyperchlorhydria. It is thought that adrenocortical hormones probably play a part in influencing normal gastric secretion.—F. E. HYTTEN

Cortisone will increase the mobilization of fats resulting in increased hepatic lipid levels under certain experimental conditions. Recent evidence indicates that total body fat content is increased by administration of this hormone. Whether these alterations in fat metabolism have any clinical significance in atherogenesis is unsettled.

The Effects of High Cholesterol Diet Alone and Plus Cortisone Administration on Phospholipid Turnover and Lipid Partition in Plasma, Liver and Aorta of Rabbits. A. Drury. *Am. J. Med. Sc.* 230: 427, 1955.

The lipid partition and plasma phospholipid turnover rates in plasma, liver and aorta were measured in three groups of experimental animals. The first group received a control diet; the second, a 1 per cent cholesterol supplemented diet, and the third, a high-cholesterol diet plus cortisone injections daily. The duration of the experiment was selected as 35 days, corresponding to one-half the time usually employed to produce atheromata formation, in order to evaluate the lipid-metabolic pattern prior to atheromata formation and to study the mechanisms involved in their pathogenesis. In the animals receiving cholesterol, with or without cortisone, a small but significant increase in aortic cholesterol was found. The cholesterol and phospholipid patterns in plasma were similar in these two groups; however, the neutral fat content of liver and plasma in the cortisone-treated group was markedly elevated. The phospholipid-specific activity of liver was similar in the three groups of animals; however, the amount of radioactive phospholipid in plasma was greater in the cortisone treated group than in the other two groups. The implications of these and other data presented are discussed in relation to the general problem of the pathogenesis of atherosclerosis. —C. R. SHUMAN

An effect of fat feedings upon blood coagulability has been demonstrated. A rise in serum lipids induced by corticosteroids may have a similar influence of enhancing blood coagulability.

Hazard of Corticotropin and Cortisone Therapy in Patients with Hypercholesteremia. D. Adlersberg, J. Stricker, and H. Himes. *J. A. M. A.* 159: 1731, 1955.

Four patients developed thrombo-embolism after institution of corticotropin or cortisone therapy for a variety of diseases (sprue syndrome, gout, rheumatoid arthritis). All patients had hypercholesteremia (above 280 mg per 100 ml). Examination of members of the three families available for study revealed familial hypercholesteremia. The authors suggest that the increased coagulability of the blood induced by the corticosteroids may, when superimposed on the metabolic defect associated with hypercholesteremia, predispose to thromboembolic diseases. They advise caution in the administration of steroid therapy to persons with high blood cholesterol levels.—S. O. WAIFE

ITEMS OF GENERAL INTEREST

Dried Breadfruit. F. E. Peters and P. A. Wills. *Nature* 178: 1252, 1956.

Breadfruit (*Artocarpus altilis* Forst.) is a staple part of the diet in many parts of the Pacific, but no means of preserving it has been described. A method for drying the fruit, used by people in the Reef Islands, is reported. The ripe fruit is cooked in ashes for an hour and, after a day, is peeled and cut into small pieces which are dried in a net over a fire. This dried fruit can be kept for 12 months. A brief chemical analysis of dried breadfruit is given.—F. E. HYTTEN

The Relationship of the Season of Birth to the State of the Primary Dentition. H. Sainsbury. *J. Dent. Research* 35: 909, 1956.

Early studies have suggested that children in northern

latitudes had more tooth decay than those in southern latitudes and that the incidence of tooth decay varied inversely with the amount of sunshine. In the present study, 300 five-year old rural children in state schools in Herefordshire, England were examined for caries and tooth structure by a rather superficial diagnostic procedure without dental explorer or radiographs. Most of these children were born in 1947 which was a year of unusual weather extremes. The temperature records for February and March were the lowest since 1895 while the months from April to November were above average. The total sunshine for the year was 86 hours below normal with only August and November above the average. Among the 40 children born in the period from December, 1946 to February, 1947, there was an average of 4.6 decayed, extracted, and filled (d.e.f.) deciduous teeth; 36 per cent of these children had conspicuously defective tooth structure. In the 58 children born between March and May, 1947, the average d.e.f. value was 3.3; 25 per cent of these children had grossly defective tooth structure. Among the 50 children born between June and August, 1947, there was an average of 3.4 d.e.f. teeth; 17.5 per cent of the children had defective tooth structure. In the next quarter from September to November, 1947, the average d.e.f. value was 3.9; 14.5 per cent of these 58 children had defective tooth structure.

While these data are not absolutely conclusive by any means, they are highly suggestive of an association between the season of birth and tooth structure and between season and dental caries susceptibility for this particular population in this year of unusual extremes.—J. H. SHAW

Hyalinosis of Skin and Mucous Membranes (Urbach-Wiethe's Lipoid-Proteinosis). H. Ungar and I. Katzenellenbogen. *A.M.A. Arch. Path.* 63: 65, 1957.

The syndrome of which about 50 cases are on record consists of disseminated areas of hyalinosis and lipid deposits in the dermis, the oral mucosa and the larynx. This paper deals with histochemical studies in a patient first described in a publication 28 years ago. There was degeneration and destruction of elastic fibers, new formation of silver fibrils throughout the dermis, hyalinosis of the upper layer of the dermis and of the oral mucosa. The hyaline is most likely a carbohydrate with little or no protein. Moderate amounts of sudanophilic material were identified. The rare condition may represent a type of generalized lipoidosis or a disturbance in protein metabolism possibly related to primary amyloidosis.—M. SILBERBERG

Age Factor and High-Fat Diets in the Evolution of Osteoarthritis in Mice. M. Silberberg and R. Silberberg. *J. Gerontol.* 12: 9, 1957.

In male mice of strain C57BL lifelong feeding of a diet enriched with 25 per cent lard advanced the onset and doubled the incidence of osteoarthritis over that seen in mice fed a stock diet containing 5 per cent fat. The high-fat diet given to weanling, young adult, or old mice for periods of five months was less injurious than if fed through life. The joints of growing mice were more susceptible to the injurious effects of the high-fat diet than those of aged mice. The decreased susceptibility of aged joints is probably related to the decrease of the growth potential of the articular tissues with advancing age.—S. SILBERBERG

An Attempt at the Interpretation of the Role of Aureomycin as a Growth Factor. C. Calet, A. Rerat, and R. Jacquot. *Compt. Rend. Acad. Sc.* 238: 1071, 1954.

The improvement in growth and in the consumption index brought about by the addition of Aureomycin to the diet of white rats can be explained neither by better digestibility of the food given, greater hydration of the tissues, nor increased protein deposition. It would appear to indicate only premature fattening.—H. GOUNELLE

Nutritional Deficiency Due to Age and Physiologic Stress; its Control by Food and Hormone W. B. Kountz, T. Kheim, P. G. Ackerman, and G. Toro. *J. Amer. Geriatrics Soc.* 4: 1005, 1956.

The authors present studies on the control of nutritional deficiency due to age and physiologic stress. The effects of thyroid, estrogens, androgens, insulin, cortisone, and corticotropin in nitrogen balance were evaluated singly and in various combinations.

The results with cortisone and corticotropin were clear-cut in that negative nitrogen balance was produced. Testosterone propionate produced positive nitrogen balance. The results obtained with thryoid, estrogens, and insulin were not impressive and were somewhat confusing. Many statements are made regarding the results which do not seem justified from the data presented.

The results are expressed as mg of nitrogen retained per kg of body weight. However, the weights of the patients are not given so it is difficult to judge how much total nitrogen was retained. In all of the studies presented the patients were in positive balance on diet alone before any hormones were given. This, plus the method of reporting the results, makes it difficult to evaluate the significance of the hormonal manipulations on nitrogen balance.—K. R. CRISPELL

Renal Hemodynamic Observations in Patients with Cystine-Storage Disease, Amino-Aciduria and Dwarfism (De Toni-Fanconi Syndrome). C. W. Daeschner, J. H. Moyer, and J. Awapara. *Am. J. Dis. Child.* 90: 623, 1955 (Soc. Trans.).

Several observers have noted that children exhibiting the syndrome of cystine storage disease, aminoaciduria, and dwarfism with hypophosphatemic glycosuric rickets show a progressive loss of renal function. This renal insufficiency is usually the cause of death. Postmortem examination of the kidney reveals a severe, generalized disease of the renal parenchyma resembling the end stage of chronic glomerulonephritis.

In the past three years the authors have had the opportunity of performing studies of renal hemodynamics function in four children with this disease. In three patients serial studies were possible, so that a total of ten renal hemodynamic studies have been performed. The diagnosis of the de Toni-Fanconi syndrome was established by the finding of hypophosphatemic rickets, hyperaminoaciduria, hyperaminoacidemia, and deposits of cystine crystals in the bone marrow and cornea. All patients showed in addition statural dwarfism, albuminuria, and intermittent glycosuria.

Renal hemodynamic studies were undertaken to study the pathogenesis of the altered renal function. Standard clearance technics using insulin and sodium para-aminohippurate (PAH) were used. The earliest defect to appear was a marked reduction in the maximum tubular excretory capacity for PAH, unassociated with a reduction in glomerular filtration rate and renal plasma flow. As the patients' disease progressed, the T_{mPAH} reached minimum values and was then followed by a progressive fall in renal plasma flow and glomerular filtration rate. In the terminal stages all moieties of renal function were severely reduced.

Massive doses of vitamin D (50,000–200,000 units daily) were given to three patients and continued until evidence of hypercalcemia appeared. This therapy produced no significant change in renal hemodynamics.

It is felt that in patients with cystine storage disease the initial renal lesion is a marked reduction in tubular mass transport and that this is then followed by a progressive loss of total renal function. Massive vitamin D therapy has not altered this course of events in the present authors' experience.—J. N. ETTELDORF

Influence of Nutrition upon Duration of Gestation in Sheep. G. Alexander. *Nature* **178**: 1058, 1956.

Groups of pregnant ewes were maintained on three planes of nutrition: high (weight gain of 200–400 g/day); medium (weight maintained); and low (weight loss of 200–400 g/day).

In general, there was a significant shortening of gestation time as the plane of nutrition was reduced. This was most consistent in those groups where regulation of diet began at the 108th or 129th day of gestation; it was less certain nearer term. "The available data also suggest that in a group of comparable ewes the heavier the uterine contents are at the time treatment is commenced, the more is parturition advanced by undernutrition. . ."—F. E. HYTTEN

Observations on the Food Habits of Myopic Children. P. A. Gardiner. *Brit. Med. J.* 2: 699, 1956.

This short paper represents a preliminary account of the dietary habits of children with myopia. Evidence is presented to show that myopic children are more fussy about their food than other children, particularly in their refusal of milk. The rate of refusal increased with the activity of the condition; those children with a rapidly deteriorating myopia have the highest rate. Although the pattern of food consumption was altered there was no evidence of dietary inadequacy.—F. E. HYTTEN

Metabolic Patterns of a Group of Overweight, Underweight and Average Weight Women. B. E. Hawthorne, W. D. Brewer, and M. A. Ohlson. *J. Nutrition* 60: 391, 1956.

The possibility that metabolic differences may exist between overweight and underweight individuals has challenged nutritionists the past three decades. Such metabolic differences do not vitiate the concept of balance between intake and outgo of energy, but it is recognized that the rate and pathways of catabolism of food may be influenced by metabolic differences.

Metabolic patterns of a group of seven overweight, seven underweight, and seven women of average weight were investigated at fasting and following two test meals of varying carbohydrate and fat composition. Respiratory quotients, hourly energy expenditures, and hourly urinary nitrogen excretions, were determined simultaneously with blood glucose, blood pyruvic acid, serum total lipids and serum chylomicron concentrations of fasting and at intervals for five hours. Although individual differences in responses were observed among all groups, certain metabolic patterns associated with the overweight and underweight subjects in this investigation were significantly greater than variations among individuals within the groups. The overweight women as a group appeared to exhibit a delay in utilization of carbohydrate in the test meals compared to the average weight and underweight women. There were some indications of a greater preference for carbohydrate in metabolism by the underweight than by the average weight women.—B. SURE